

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF TEXAS
CORPUS CHRISTI DIVISION**

MARIA LUISA GARZA, INDIVIDUALLY
AND
OSCAR GARZA, SR., INDIVIDUALLY

VS.

WYETH, LLC f/k/a WYETH d/b/a
WYETH INC., ET AL.

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CIVIL ACTION NO. 2:12cv00198

JURY REQUESTED

**APPENDIX TO
MEMORANDUM OF LAW IN SUPPORT OF
DEFENDANT TEVA PHARMACEUTICALS USA, INC.'S
MOTION FOR SUMMARY JUDGMENT**

| Exhibit No. | Description of Document | Appendix Page Nos. |
|--------------------|---|--|
| 1 | Transcript of Initial Conference, Dec. 21, 2012 | App. Pg. 1 |
| 2 | April 22, 2003 FDA approval letter for Reglan [®] | App. Pg. 29 |
| 3 | July 26, 2004 FDA approval letter for Reglan [®] | App. Pg. 31 |
| 4 | FDA-approved revised Reglan [®] label | App. Pg. 34 |
| 5 | Affidavit of Philip Erickson Ex. A: June 24, 2005 letter to FDA Ex. B: June 24, 2005 letter to FDA Ex. C: July 20, 2009 letter to FDA Ex. D: July 20, 2009 letter to FDA Ex. E: Excerpt from NDC Directory | App. Pg. 45 App. Pg. 47 App. Pg. 79 App. Pg. 81 App. Pg. 185 App. Pg. 188 |
| 6 | June 30, 2009 FDA approval letter for Reglan [®] | App. Pg. 190 |
| 7 | FDA-approved revised Reglan [®] label | App. Pg. 194 |
| 8 | Regulatory event timeline | App. Pg. 230 |
| 9 | Plaintiff Maria Luisa Garza's pharmacy records | App. Pg. 231 |
| 10 | Summary chart of pharmacy records | App. Pg. 243 |
| 11 | Declaration of Michael A. Walsh | App. Pg. 244 |

Respectfully submitted,

/s/ Michael A. Walsh

Michael A. Walsh

Texas State Bar No. 00790146

SD Texas Bar No. 21846

STRASBURGER & PRICE, LLP

901 Main Street, Suite 4300

Dallas, TX 75202
Phone: 214-651-4300
Fax: 214-651-4330
E-mail: michael.walsh@strasburger.com

Jonathan I. Price
GOODWIN PROCTER LLP
The New York Times Building
620 Eighth Avenue
New York, New York 10018
Phone: 212-813-8800
Fax: 212-355-3333
E-mail: JPrice@goodwinprocter.com

Richard A. Oetheimer
GOODWIN PROCTER LLP
Exchange Place
53 State Street
Boston, MA 02109
Phone: 617-570-1000
Fax: 617-523-1231
E-mail: ROetheimer@goodwinprocter.com

**ATTORNEYS FOR DEFENDANT TEVA
PHARMACEUTICALS USA, INC.**

CERTIFICATE OF SERVICE

I hereby certify that on April 23, 2013, a copy of the foregoing was filed electronically. Notice of this filing will be sent to all parties by operation of the Court's electronic system. Parties may access this filing through the Court's system.

/s/ Michael A. Walsh

Exhibit 1

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF TEXAS
CORPUS CHRISTI DIVISION

MARY JACKSON, ET AL.,) CASE NO: 2:12-CV-196
)
Plaintiffs,) CIVIL
)
vs.) Corpus Christi, Texas
)
WYETH, LLC, ET AL.,) Friday, December 21, 2012
)
Defendants.) (9:03 a.m. to 9:35 a.m.)

MARIA LUISA GARZA, ET AL.,)
)
Plaintiffs,)
)
vs.) CASE NO: 2:12-CV-198
)
WYETH, LLC, ET AL.,)
)
Defendants.)

INITIAL CONFERENCE

BEFORE THE HONORABLE NELVA GONZALES RAMOS,
UNITED STATES DISTRICT JUDGE

Appearances: See next page
Court Recorder: Genay Rogan
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APPEARANCES FOR 2:12-CV-196:

Mary Jackson, et al.: ROBERT BRZEZINSKI, ESQ.
J. THOMAS RHODES, III, ESQ.
Rhodes Law Firm
126 Villita St.
San Antonio, TX 78205

Wyeth and Pfizer: MICHAEL R. KLATT, ESQ.
816 Congress Ave., Suite 1510
Austin, TX 78701

Schwarz Pharma: QUINNCY N. MC NEAL, ESQ.
Mayer Brown
700 Louisiana St., Suite 3400
Houston, TX 77002

Teva Pharmaceuticals: MICHAEL A. WALSH, ESQ.
Strasburger Price
901 Main, Suite 4300
Dallas, TX 75202

Generics Bidco, et al: JORGE C. RANGEL, ESQ.
615 N. Upper Broadway, Suite 2020
Corpus Christi, TX 78401

APPEARANCES FOR 2:12-CV-198

Maria Garza, et al.: J. THOMAS RHODES, III, ESQ.
Rhodes Law Firm
126 Villita St.
San Antonio, TX 78205

Wyeth and Pfizer: MICHAEL R. KLATT, ESQ.
816 Congress Ave., Suite 1510
Austin, TX 78701

Schwartz Pharma: QUINNCY N. MC NEAL, ESQ.
Mayer Brown
700 Louisiana St., Suite 3400
Houston, TX 77002

Teva Pharmaceuticals: MICHAEL A. WALSH, ESQ.
Strasburger Price
901 Main, Suite 4300
Dallas, TX 75202

APPEARANCES FOR 2:12-CV-198 (Continued)

Watson Pharma, et al.: REX A. LITTRELL, ESQ.
Ulmer Berne
88 E. Broad St., Suite 1600
Columbus, OH 43215

Corpus Christi, Texas; Friday, December 21, 2012; 9:03 a.m.

(Call to Order)

THE COURT: Court calls Cause Number C-12-196,
Jackson, et al. versus Wyeth, et al.

MR. BRZEZINSKI: Good morning, your Honor.

THE COURT: Good morning.

MR. BRZEZINSKI: Robert Brzezinski and Tom Rhodes for
the plaintiff.

THE COURT: Good morning.

MR. WALSH: Judge, Mike Walsh for Defendant TEVA
Pharmaceuticals.

MR. MCNEAL: Your Honor, Quincy McNeal for Defendant,
Schwarz Pharma.

MR. LITRELL: Your Honor, I'm Rex Littrell for the
PLIVA, Barr, and Watson defendants, but I am actually not in
Jackson; we're in *Garza*.

THE COURT: Right. Okay. And I was going to try to
clean that up in a minute.

MR. KLATT: Your Honor, Mike Klatt for Pfizer and
Wyeth in both the *Jackson* and the *Garza* cases.

MR. RANGEL: Your Honor, Jorge Rangel for Defendant
Generics Bidco in *Jackson*. We are not in *Garza*.

THE COURT: You're -- okay. Let me go ahead and call
the other case, too, and let's flesh out the parties and then
we can proceed. So, then, C-12-198 is *Garza, et al. versus*

1 *Wyeth, et al.* And I know there was a dismissal or a
2 stipulation dismissing some of the defendants on *Jackson* but
3 not *Garza*.

4 **MR. BRZEZINSKI:** That's correct, your Honor.

5 **THE COURT:** And I think those were Watson, Barr --

6 **MR. LITTRELL:** Yes, your Honor.

7 **THE COURT:** -- PLIVA, and Qualitest, which is really
8 you, Mr. Rangel, as Bid -- Bidco, right?

9 **MR. RANGEL:** Yes, your Honor.

10 **THE COURT:** So, you all are not in the *Jackson* case.

11 **MR. LITTRELL:** Correct.

12 **THE COURT:** And they're going to remain in the *Garza*
13 case for now, at least, or --

14 **MR. BRZEZINSKI:** That's correct, your Honor.

15 **THE COURT:** Okay. Can we address these cases
16 together even though -- understanding that some parties are
17 involved in one and not the other?

18 **MR. BRZEZINSKI:** That would be fine with us, your
19 Honor.

20 **THE COURT:** Okay.

21 **MR. WALSH:** And, your Honor, if I might add,
22 Mr. Littrell is -- will be arguing the pre-emption issues. The
23 issues are the same in both cases, so, because he's probably
24 the most knowledgeable person --

25 **THE COURT:** Okay.

1 **MR. WALSH:** -- in the country on the issue, it would
2 make more sense for you to hear from him.

3 **THE COURT:** All right. And we're going to argue the
4 motions to dismiss. Let me just, before we get there -- on the
5 scheduling order, obviously, the one that had been proposed is
6 not appropriate at this point. So, let's proceed on the
7 argument on the motion to dismiss, and then we can address the
8 scheduling order.

9 **MR. LITRELL:** Good morning, your Honor.

10 **THE COURT:** Good morning.

11 **MR. LITRELL:** Again, I'm Rex Littrell for PLIVA and
12 the Barr defendants and the Watson defendants. I am not the
13 most knowledgeable person about pre-emption in the country, but
14 I'll take that as a little Christmas gift from Mr. Walsh.

15 We are here this morning on motions to dismiss filed
16 in both cases, and I would just argue for both of them because
17 the issues are the same. Basically --

18 **THE COURT:** And let me just be clear, though. Then,
19 the motions to dismiss on *Jackson*, it's TEVA and Bidco, and on
20 *Garza* it's Barr and TEVA, correct?

21 **MR. LITRELL:** It's actually all of the defendants
22 have now joined the motion in *Garza*.

23 **THE COURT:** Okay.

24 **MR. LITRELL:** It was originally filed by two, I
25 believe, and then everyone else joined.

1 **THE COURT:** Okay. You can proceed.

2 **MR. LITTRELL:** Thank you, your Honor.

3 What the plaintiffs -- the issue before us this
4 morning is federal pre-emption, obviously, and the impact of
5 the United States Supreme Court in *Mensing versus PLIVA*.
6 Generally, what both plaintiffs have alleged in their
7 complaints is that they were injured as a result of the
8 ingestion of the medication metoclopramide, brand name Reglan;
9 the generic form is known as metoclopramide. They've sued both
10 the manufacturers of the brand name drug and then, of course,
11 the generics, and they assert a number of causes of action for
12 negligence, strict liability, breach of implied warranties,
13 misrepresentation, suppression of evidence and fraud, and then
14 deceptive trade practices.

15 As the generic defendants have set forth in their
16 briefs, we believe all of those claims are pre-empted by
17 federal pre-emption under the Supreme Court's decision in
18 *Mensing*. That case involved the same drugs, it involved the
19 same alleged injury, it involved most of the same parties, and
20 even some of the counsel are the same in both cases. And it is
21 a decision that since its come out has been applied by courts
22 throughout the country to dismiss state law tort claims against
23 generic drugs manufacturers. The second ground for the
24 generics' motion is that we believe the claims are also barred
25 under Section 82.007 of the Texas Civil Practice and Remedies

1 Code. And I'll address both of those briefly.

2 *Mensing* we believe is the controlling decision
3 regarding personal injury cases against generic drug
4 manufacturers. In *Mensing* the Supreme Court considered whether
5 state law tort claims against generic manufacturers are pre-
6 empted by federal law. They considered that issue at the
7 motion to dismiss stage, and it found that the lawsuits had to
8 be dismissed because federal pre-emption did apply, and it
9 dismissed -- or ordered the lower courts to dismiss the
10 lawsuits in their entirety. Those complaints in *Mensing*, which
11 actually were two cases, *Mensing* and another case called
12 *Dimensi* [sic] out of the -- *Demahy* out of the Fifth Circuit --
13 both also alleged the same claims that we see here, the same
14 wide range of state tort law claims.

15 And, again, what the Supreme Court really found was
16 that in the pharmaceutical context that all claims against drug
17 manufacturers really boil down to failure-to-warn claims. That
18 underlying analysis in *Mensing* is consistent with what Texas
19 courts have held under Texas state law. They have also held
20 that all claims, no matter how articulated, in a pharmaceutical
21 case really boil down to failure-to-warn claims; should the
22 labeling have provided some additional or different warning
23 than what it provided.

24 And while the *Mensing* decision was hotly disputed
25 amongst the justices -- it was a 5-4 decision -- the one thing

1 that all the justices agreed about was its broad impact. The
2 majority said that they recognized the unfortunate hand that
3 they were dealing to people who took generic drugs, but they
4 felt they were forced to do so by the federal regulatory
5 scheme. The dissenters also agreed in the dissent that the
6 impact of the decision was to stop litigation against generic
7 drug manufacturers, which, of course, they didn't want to
8 happen. That's why they were in the dissent.

9 This decision has been applied by a number of judges
10 here in the Southern District of Texas. We have provided your
11 Honor with the *Del Valle* decisions, which were both the
12 magistrate judge and the district judge decision; the *Farris*
13 (phonetic) decision, and the *Eckhardt* decision. All discuss
14 *Mensing*, and a couple of those also discuss Section 82.007.
15 The claims also were recently revisited by the Fifth Circuit in
16 the *Demahy* case. The case went back down after *Mensing* was
17 dismissed by the district court. The plaintiff disputed that
18 dismissal, said that all claims should not have been dismissed.
19 That went back to the Fifth Circuit. The Fifth Circuit again
20 found that all claims had to be dismissed. That decision is
21 consistent with other circuit court decisions, federal circuit
22 courts, by the Sixth Circuit, the Eighth Circuit, and the Ninth
23 Circuit, and then all of the numerous other decisions that we
24 cited for your Honor is in the briefs.

25 So, looking at it in terms of this case and this

1 particular complaint, which I can tell your Honor is very
2 similar to the *Mensing* complaint in terms of its allegations,
3 the core of the plaintiffs' complaint is very clearly set
4 forth. They say this case involves the drug companies
5 defendants' failure to warn doctors of -- and patients of
6 information within their knowledge or possession regarding
7 Reglan. They also say that their injuries came about as a
8 foreseeable and proximate result of the drug company
9 defendants' dissemination of inaccurate, misleading, material
10 incomplete and false information. And, then, finally they say
11 that the generic defendants failed to use reasonable care to
12 modify the package inserts for the drugs. Those are exactly
13 the claims that were at issue in *Mensing* and that is why the
14 case is directly applicable.

15 As Judge Morgan said in *Del Valle*, this kitchen sink
16 approach does not obscure the fact that all of these claims are
17 based upon the purported failure of the generic drug defendants
18 to warn of the dangerous of the long-term use of the drug.
19 That's the same claims here. As I indicated, that's consistent
20 with Texas law, which finds that all claims in the
21 pharmaceutical context were failure-to-warn claims; that was
22 most recently confirmed by the Texas Supreme Court in *Centocor,*
23 *Inc. versus Hamilton*. That was a case dealing with the learned
24 intermediary doctrine, but again the Texas court -- Supreme
25 Court made clear that all of these claims are failure-to-warn

1 claims, and also the *Farris* decision and the *Eckhardt* decision
2 also, again, made clear that that's the case under Texas law.

3 So, in short, Texas defines all of these claims as
4 failure-to-warn claims, and *Mensing* says that all failure-to-
5 warn claims against generic drug defendants are pre-empted by
6 federal law, and that's why it applies here.

7 So, what we've seen in the briefing is some attempt
8 by plaintiffs to plead around *Mensing* or to attempt to assert
9 arguments around *Mensing*. And they've raised some theories
10 that aren't in their Complaint but they've tried to raise in
11 their briefing. There is a claim that the generic defendants
12 failed to communicate information to doctors. It's clearly a
13 failure-to-warn claim, but it's just put a different way. It's
14 also completely inconsistent with their allegations that are
15 actually in their complaint. This argument is that we didn't
16 provide any information, they say in their briefs, to the
17 doctors. And yet their complaint says that the doctors
18 prescribed the brand name drug, Reglan, that the defendants
19 provided information to doctors about Reglan, metoclopramide,
20 and that that information was somehow false or misleading or
21 otherwise inaccurate. So, the whole failure-to-communicate
22 theory is completely inconsistent with the allegations in their
23 complaint, and for that reason the Court in *Eckhardt* dismissed
24 the theory finding that it's inconsistent with the complaint.

25 In the *Del Valle* case here out of the Southern

1 District, that theory was also discussed from a different point
2 of view. And the judge there said that really that claim
3 remains a failure-to-warn claim because all communications with
4 doctors really are labeling. I know that's an issue your Honor
5 recently addressed in a different context, not involving a
6 generic drug manufacturer, but it was -- it was one of the
7 bases for the high quoting in *Del Valle*. And, so, what we've
8 provided to your Honor are a number of other court decisions
9 that also discuss and reject that failure-to- communicate
10 theory.

11 We also have asserted -- the plaintiffs have asserted
12 in their briefs what's sometimes referred to as a "failure-to-
13 update theory," the idea that certain generic manufacturers did
14 not update their label when changes were made to the brand name
15 drug, Reglan.

16 **THE COURT:** And I think that's probably where most of
17 my questions are.

18 **MR. LITRELL:** Okay. And that -- and that's fine.

19 **THE COURT:** I mean, not that I have questions right
20 now, but that's probably --

21 **MR. LITRELL:** And that makes sense, your Honor.
22 What's interesting about it is, first of all, it's not in the
23 plaintiffs' complaint. That's, again, an issue that we see.
24 It's not an allegation raised in their complaint, in their
25 amended complaints, including the amended complaint that was

1 recently filed.

2 **THE COURT:** Well, let's assume that it's going to be.

3 **MR. LITTRELL:** Okay. Let's assume that. Then the
4 issue becomes: Who are they alleging it against? In their
5 brief they are asserting it only against PLIVA, one of the
6 defendants, not against the other generic drug manufacturers.
7 It's interesting; obviously, TEVA has been dismissed from the
8 *Jackson* case because there was no product ID. Actually, I
9 don't believe there is any product ID for PLIVA either in the
10 *Garza* case, but that's an issue that can be dealt with in a
11 different context, but the argument is raised against PLIVA.

12 So, what did the Supreme Court do with this failure-
13 to-update claim? We know that the Supreme Court deals with
14 federal pre-emption issues all the time. They deal with them
15 in all kinds of contexts; drug cases, medical device cases,
16 cigarette cases, labor cases. And we also know that the
17 Supreme Court always goes out of its way to try to defer the
18 state law where it can. In *Mensing*, this failure-to-update
19 issue was brought to the attention of the Supreme Court prior
20 to oral arguments when it was discovered that the labels didn't
21 match. And yet neither the majority nor the dissent
22 articulated any sort of exception to federal pre-emption based
23 upon this failure-to-update theory. And that's particularly
24 interesting with respect to the dissent, because the dissenters
25 were clearly highly incentivized to try to find exceptions to

1 the broad impact of *Mensing*. In fact, in one point of the
2 dissent they went out of their way to talk about a different
3 form of generic drugs where a brand manufacturer sets up a
4 company that also makes a generic form of the drug. And the
5 dissenters said: That's not covered by this opinion. So, they
6 were looking for exceptions. I'm not saying the dissent was
7 correct about that distinction, but it demonstrates that they
8 were looking for examples of potential exceptions to the broad
9 impact.

10 **THE COURT:** So, it wasn't addressed either way.

11 **MR. LITRELL:** That's correct. And the question
12 becomes: Why didn't they address it? And I think that there
13 is a -- there is a reason for that. I believe that all of the
14 justices on the Supreme Court recognize that this failure-to-
15 update issue is not an issue of state law; it's an issue of
16 federal law. There is no requirement in Texas state law or any
17 other state law that says that a generic drug's package insert
18 has to match a brand name drug's package insert. That
19 obligation arises solely from the Food, Drug, and Cosmetic Act,
20 the FDCA, a federal act. But the FDCA expressly provides that
21 you cannot have private rights of actions for violations of the
22 FDCA. And, in fact, the Supreme Court in the *Buckman* decision
23 that we cited for your Honor specifically held that. They said
24 that the FDCA is clear that only the federal government can
25 bring a cause of action for alleged violations of the FDCA.

1 And, so, I believe that the reason the Supreme Court
2 didn't deal with this issue is they don't think it impacts
3 federal pre-emption. They recognize that it is an issue of
4 federal law for which a private litigant cannot bring a cause
5 of action.

6 Many other courts have acknowledged that -- that
7 issue with regard to failure to update, and they have also
8 focused on another issue that arises in the context of these
9 complaints. The plaintiffs allege in both of their complaints
10 that the brand name and generic metoclopramide labeling
11 remained inadequate through 2009. They say that due to the
12 inadequate nature of the drugs, the FDA in 2009 took action to
13 insert a black box. So, if you try to apply this failure-to-
14 update theory to PLIVA post-2004, which is what the theory is
15 in their briefs, the plaintiffs are really telling your Honor
16 that under Texas law PLIVA had a duty to provide an inadequate
17 warning, what they say is an inadequate warning, to users -- to
18 doctors and users of the drugs. There is no such claim in
19 Texas. There is no such claim in any state law. And, in fact,
20 a number of courts have dismissed the failure-to-update theory
21 on that ground, that you can't say the label was inadequate
22 even after 2004 and at the same time claim that a drug company
23 had a duty to provide that inadequate warning to doctors.

24 So, the theory has been rejected. It was, by the
25 way, as we set forth in the briefs, it was presented to both

1 the Sixth Circuit and the Eighth Circuit after *Mensing*. In
2 fact, the Sixth Circuit had a trio of cases all under the
3 umbrella name of *Smith versus Wyeth* that were before the Sixth
4 Circuit when *Mensing* was decided, and before it issued its
5 decision the Sixth Circuit said: We want briefing on this
6 issue; tell us that there are claims that survived *Mensing*.
7 The parties then submitted briefs. They articulated -- the
8 plaintiffs articulated this argument and the Sixth Circuit
9 issued a decision still dismissing them. The plaintiffs then
10 filed a petition for rehearing and a rehearing en banc where
11 again they argued this issue and basically told the Sixth
12 Circuit: We think you missed this issue. And the Sixth
13 Circuit for a second time issued an order saying: Every judge
14 on the panel has looked at your brief and we agree that the
15 petition should be denied. That's the Sixth Circuit.

16 The Fifth Circuit it's also been raised in post-
17 *Mensing* briefing in *Demahy* that the Fifth Circuit did not
18 accept that argument, and neither did -- I'm sorry. I take
19 that back, your Honor. That was the Eighth Circuit where it
20 was raised, not the Fifth Circuit. The *Demahy* case didn't have
21 that allegation when it went back down to the Fifth Circuit.
22 But it has been addressed in a number of courts here in Texas
23 and in other district courts in the Fifth Circuit's area. So
24 we believe that theory is also gone and that all of the claims
25 again eventually remain failure-to-warn claims.

1 The claims also then, the defendants contend, are
2 barred by 82.007. That is a issue that was brought up by the
3 Courts in *Del Valle* and *Farris*. That statute provides that you
4 can't have claims, pharmaceutical claims, against drugs in the
5 pharmaceutical context. There are exceptions. The Fifth
6 Circuit has addressed the exception that the plaintiffs allege
7 in their complaints here, which is basically a fraud on the FDA
8 claim. The plaintiffs in their complaints expressly state that
9 82.007 should not be applied because the defendants made
10 misrepresentations to the FDA. The Fifth Circuit found in the
11 *Lofton versus McNeil Consumer and Specialty Pharma* case that
12 came out this year that that fraud on the FDA exception is pre-
13 empted by federal law, that to proceed on that, that exception
14 to 82.007, you would have to show that the FDA actually found
15 that the defendant had committed fraud. There is no
16 allegation, in fact, of that here; and, in fact, I could tell
17 you that's never happened against any of these manufacturers
18 for metoclopramide. And this litigation has been going on a
19 long time. I know there is a request for discovery on that. I
20 think it's really just an attempt to kick the ball down the
21 field a little longer to try to drag things out, but there is
22 no such issue in this case.

23 So, unless your Honor has other questions about that
24 or any of the other claims, that really is the defendants'
25 position in a nutshell.

1 **THE COURT:** All right. Thank you.

2 **MR. LITTRELL:** Thank you.

3 **MR. BRZEZINSKI:** May I proceed, your Honor?

4 **THE COURT:** Yes.

5 **MR. BRZEZINSKI:** Robert Brzezinski for the

6 plaintiffs, your Honor.

7 Judge, there are courts out there, including courts
8 in the Fifth Circuit, that have declined to follow in lockstep
9 with the reasoning used in the opinions that Mr. Littrell
10 cites. As far as one of the cases relied upon most heavily by
11 the defendants in their motions and their reply to our
12 response, namely, the *Demahy* case, we don't spend a lot of time
13 addressing *Demahy*, Judge, in our response, for one thing,
14 because page one of the Court's opinion in that case expressly
15 states that it's unpublished and it's not precedent. We agree
16 that *Demahy* follows suit with the other courts who have ruled
17 that the plaintiffs' claims against generic manufacturers were
18 pre-empted. However, even the *Demahy* court mentions that the
19 rulings of pre-emption have not been unanimous in favor of the
20 generic manufacturers.

21 And the *Demahy* court, in fact, cites to a case called
22 *Cooper versus Wyeth* as an exception to the decisions finding in
23 favor of the generic manufacturers in a broad sense. The
24 *Cooper* court judge -- that was the district court in Louisiana,
25 Fifth Circuit district court -- that court held that the

1 plaintiff's claims that the generic manufacturers failed to
2 label their products with the FDA labels that were required of
3 the brand name manufacturers at that time would violate federal
4 law and likely state law as well. I think Mr. Littrell
5 characterized it as a failure-to-update claim. That's really
6 the crux of the *Cooper* opinion.

7 In that situation, the *Cooper* court reasoned that the
8 requirements of state law would co-extend with but would not
9 exceed the requirements of federal law, rendering impossibility
10 of pre-emption inapplicable. And the Court further stated that
11 nothing in the *Mensing* decision forbids that result and then
12 referenced two other decisions, one from the Western District
13 of North Carolina, which is *Cook versus Wyeth*, and one from
14 South Carolina, *Fisher versus Pelstring*, both of which have
15 held that *Mensing's* impossibility analysis for pre-emption was
16 inapplicable to claims that generic manufacturers failed to
17 update their labels, and that's the Reglan label, mandated by
18 the FDA. And, thus, the *Cooper* court ruled, Judge, that the
19 claim by the plaintiffs was not pre-empted in that sense and
20 that the generic motion -- generic defendants' motion to
21 dismiss on that ground was denied.

22 And, Judge, I disagree that we haven't pled this.
23 We've alleged in our pleadings in both of these cases that the
24 defendants disseminated inaccurate, misleading, materially
25 incomplete and/or inadequate information. And we give as a

1 specific example the 2009 box warning mandated by the FDA. And
2 we plead further that the plaintiff was not made aware or given
3 the benefit of these enhanced warnings. And we'd submit that,
4 as with *Cooper* and the other cases holding similarly, the
5 *Mensing* pre-emption ruling is inapplicable to the claim by the
6 plaintiffs in the *Jackson* case and the *Garza* case regarding the
7 failure to update the defendants' labels in accordance with FDA
8 mandates. And, therefore, their claims in that respect are not
9 pre-empted.

10 To the extent that the Court feels that these claims
11 are insufficiently pled, we would ask the Court under *Stover*
12 *versus Hattiesburg Public School*, which is 549 F.3d 985, to
13 find that the plaintiffs' argument in that respect be
14 considered a motion to amend under Federal Rules of Civil
15 Procedure 15(a) and to allow us to go plead the claims more
16 specifically.

17 The -- as far as the rest of the points raised by
18 Counsel, the other claims asserted by the plaintiff against the
19 generic defendants, in other words, the claims against the
20 generic manufacturers other than those for failing to update
21 their labels, Judge, I'm going to be totally candid with you
22 and say that unless you want to take the novel approach of
23 ruling in contravention of many of the decisions issued since
24 *Mensing*, defense counsel is probably correct on the pre-emption
25 in that sense. But that still leaves the issue of the failure

1 of these generic manufacturers to update their labels, and I'd
2 urge you under *Cooper* and the logic used in *Cook* and *Fisher* to
3 find that the claims of Mrs. Garza and Mrs. Jackson are not
4 pre-empted in respect to the failure to update, and to deny
5 these defendants' motions to dismiss on that point.

6 **THE COURT:** All right. Thank you.

7 **MR. BRZEZINSKI:** Thank you, Judge.

8 **THE COURT:** Anything further?

9 **MR. LITTRELL:** No, your Honor.

10 **THE COURT:** I'm not going to rule today because I
11 want to look at the issue a little further, but if, in fact,
12 their pleading is not sufficient, I'm going to allow them to
13 amend, so -- okay. Nothing further on that.

14 I don't know if you all want to wait to address a
15 trial until after there is a decision on this or if you want to
16 go ahead and at least get a trial date.

17 **MR. BRZEZINSKI:** Judge, we'd prefer to get a trial
18 date.

19 **THE COURT:** Probably better.

20 **MR. LITTRELL:** Your Honor, I think it would be the
21 generic's position that we would prefer to wait until after
22 your Honor ruled and then we'd know what claims were left and
23 know -- have a better idea of what time period we need to
24 address any claims that might remain. But at the same time, we
25 can deal with a schedule if that's how your Honor would like to

1 proceed.

2 **MR. BRZEZINSKI:** I don't know what the Court's trial
3 schedule is, but, you know, depending on how far out we're
4 looking, I think it can be accommodated either way.

5 **THE COURT:** Yeah; and how much time generally do you
6 all think you all might need before you are ready for trial, or
7 when are you looking at trial?

8 **MR. LITTELL:** Your Honor, the defendants were
9 playing with some dates amongst ourselves, when we were looking
10 at staggering both of the cases, looking at trial dates maybe
11 in March and April of 2014. Usually we need a -- to gather
12 medical records and then follow up from there, we usually need
13 about a year, and then we need some time for briefing.

14 **THE COURT:** Okay.

15 **MR. KLATT:** Your Honor, could I address one issue
16 that I think --

17 **THE COURT:** Yes.

18 **MR. KLATT:** -- hasn't been discussed yet? Mr. McNeal
19 and I represent the brand name manufacturers.

20 **THE COURT:** Uh-huh.

21 **MR. KLATT:** We're not affected by the --

22 **THE COURT:** Right.

23 **MR. KLATT:** -- *Mensing* pre-emption decision or the
24 motion to dismiss, but what -- what does govern us is the line
25 of cases generally called the "*Foster*" cases, which basically

1 say that if your product wasn't involved in the case, then you
2 get out. Ten Texas courts, including three federal courts in
3 the Southern District, have granted summary judgment within the
4 last five months on that.

5 One of those cases, the *Del Valle* case, is now on
6 appeal in the Fifth Circuit, which insofar as the brand
7 manufacturers are concerned *Del Valle* will be -- whatever the
8 Fifth Circuit does there will be dispositive as to the brand
9 manufacturers. We expect the Fifth Circuit, if they follow
10 their normal course, to rule probably this coming summer on *Del*
11 *Valle*. The appellants have submitted their brief. The
12 defendants submit their brief the first week in January. Oral
13 argument will follow, and then the Fifth Circuit, presumably,
14 will render their decision. And whatever the Fifth Circuit
15 decides, if -- if they affirm the summary judgments from the
16 other judges in the Southern District, then, obviously, we
17 would just file the same motion tracking that decision. If
18 they deny it, then the case at that point would be appropriate
19 to proceed against us, but what we would request is that we
20 hold off until we see exactly what the Court does so we --
21 neither side has to engage in any briefing when we really don't
22 know what the Fifth Circuit is going to do.

23 **THE COURT:** Right. Mr. Brzezinski or Mr. Rhodes?

24 **MR. RHODES:** Your Honor, with respect to the
25 scheduling issue, I think a year is plenty of time to get this

1 case ready, and I would respectfully suggest that we shouldn't
2 be put on hold until the Fifth Circuit comes out. If the Fifth
3 Circuit goes the way they want it to go, then, you know, all
4 they've done is do a little extra work and then they -- they
5 walk away from it. If the Fifth Circuit doesn't go that way, I
6 don't want to have wasted six months on waiting on some opinion
7 to come out. So, I think that if we -- if we engage in
8 meaningful discovery, we can -- we can get this case ready by
9 November or December of next year fairly easily.

10 **THE COURT:** And, really, you all aren't that far --
11 March of '14 to the summer of, you know, '13 is not that far
12 apart.

13 **MR. KLATT:** I think the whole point, your Honor, is
14 we don't want to have to walk away from work that we didn't
15 need to do. The case was in --

16 **THE COURT:** Um -- yeah.

17 **MR. KLATT:** The case was in state court for a year
18 and the plaintiffs took no action whatsoever. So, what we'd
19 simply ask is that -- you know, we'll proceed -- we'll be ready
20 to proceed as soon as the Fifth Circuit rules one way or the
21 other.

22 **THE COURT:** I'm not inclined to wait on that.

23 **MR. KLATT:** And if the Court would rather, we can
24 file a formal motion to stay laying out in more detail our
25 arguments.

1 **THE COURT:** You can do that if you'd like. I just --
2 I think we need to go ahead and just set a trial date on this.

3 **MR. RHODES:** Well, Judge, you know, we could split
4 the difference and do it, like, in January.

5 **THE COURT:** I know. We can see what we have.
6 Brandy?

7 **THE CLERK:** January 13th, 2014.

8 **MR. RHODES:** That works for us.

9 **MR. BRZEZINSKI:** Fine with us. If the world is still
10 here, Judge.

11 **(Laughter)**

12 **MR. LITTRELL:** I think we're safe on that regard. I
13 think (indiscernible) in other parts of the world really are
14 who is (indiscernible).

15 **THE COURT:** Well, isn't today a significant day --

16 **MR. LITTRELL:** Yes.

17 **THE COURT:** -- in the Mayan calendar?

18 **(Laughter)**

19 Any -- okay. We'll go ahead and set a trial date and
20 we'll see where we are. And, you know, I probably -- it will
21 probably be into mid to late January before I have a ruling on
22 your motion to dismiss; hopefully, mid January.

23 **MR. KLATT:** Your Honor, would you -- would you like
24 for the brand name defendants to go ahead and file a motion for
25 summary judgment that tracks the issues that are pending in

1 front of the Fifth Circuit, or would you like us to hold off
2 until the Fifth Circuit rules?

3 **THE COURT:** You can probably wait on it, because
4 that's probably what I'm going to do, refile it, so --

5 **MR. KLATT:** Okay. In other -- I'm sorry, your Honor.
6 You would wait until the Fifth Circuit rules to see --

7 **THE COURT:** Yeah; you --

8 **MR. KLATT:** Okay. We'll --

9 **THE COURT:** No, you don't have to file it right now.

10 **MR. KLATT:** Okay.

11 **THE COURT:** That way it doesn't start my time period
12 running on my motions pending.

13 **(Laughter)**

14 So, anything else to address this morning?

15 **MR. LITTRELL:** Your Honor, are you considering trying
16 the cases together, or would you like to have staggered trial
17 dates for the two cases?

18 **THE COURT:** You all were recommending staggered trial
19 dates.

20 **MR. LITTRELL:** Yes.

21 **THE COURT:** Anything from the plaintiffs on that?

22 **MR. BRZEZINSKI:** Judge, I think the issues are so
23 similar that they ought to be tried together.

24 **MR. RHODES:** The only --

25 **THE COURT:** Is there a reason not to try them

1 together? Just because I imagine it will take some time.

2 **MR. KLATT:** There is a line of cases, your Honor,
3 that say generally cases of these nature, which involve
4 completely separate issues, of completely separate medical
5 histories, medical facts, generally should not be tried
6 together. But, obviously, we hadn't briefed that at this
7 point.

8 **THE COURT:** Okay. Well, maybe you all can look into
9 that.

10 **MR. WALSH:** Yes, Judge. What I would add is perhaps
11 this is premature for that issue. Maybe once we get through
12 the discovery phase we would know better how to address it.

13 **THE COURT:** Okay. Well, this date will be for both
14 cases, and we can address that issue as we go along. How about
15 that?

16 **MR. RHODES:** Thank you, your Honor.

17 **THE COURT:** Anything else for this morning?
18 Plaintiff? Defense?

19 **MR. SPEAKER:** Nothing from us.

20 **MR. LITTRELL:** No, your Honor.

21 **MR. SPEAKER:** No, your Honor.

22 **THE COURT:** All right. Thank you.

23 **MR. LITTRELL:** Thank you.

24 **MR. SPEAKER:** Thank you. Happy holidays, Judge.

25 **THE COURT:** Thank you. You all, too.

MR. SPEAKER: Thanks, Judge.

(This proceeding was adjourned at 9:35 a.m.)

CERTIFICATION

I certify that the foregoing is a correct transcript from the electronic sound recording of the proceedings in the above-entitled matter.



Signed

January 7, 2013

Dated

TONI HUDSON, TRANSCRIBER

Exhibit 2



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-854/S-040

Schwartz Pharma, Inc.
Attention: Donna K. Multhauf, Director
Regulatory Affairs and Quality Assurance
6140 W. Executive Drive
Mequon, WI 53092

Dear Ms. Multhauf:

Please refer to your supplemental new drug application dated August 25, 2000, received August 28, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reglan[®] (metoclopramide, USP) Tablets, 5 mg and 10 mg.

Your submission of October 22, 2002, constituted a complete response to our February 28, 2001, action letter.

This supplemental new drug application provides for the addition of a **Geriatric Use** subsection to the **PRECAUTIONS** section of the package insert and deletes information relating to Reglan[®] Syrup and Reglan[®] Injectable products.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on October 22, 2002.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Susan Daugherty, Consumer Safety Officer, at (301) 827-7475.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joyce Korvick
4/22/03 01:47:42 PM
for Dr. Robert Justice

Exhibit 3



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-854/S-047

CBE-0 SUPPLEMENT

Schwartz Pharma, Inc.
Attention: Donna K. Multhauf, Director
Regulatory Affairs and Quality Assurance
6140 W. Executive Drive
Mequon, WI 53092

Dear Ms. Multhauf:

Please refer to your supplemental new drug application dated February 24, 2004, received February 24, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reglan[®] (metoclopramide, USP) Tablets, 5 mg and 10 mg.

This "Changes Being Effected" supplemental new drug application provides for revisions to the **PRECAUTIONS, INDICATIONS AND USAGE**, and **DOSAGE AND ADMINISTRATION** sections of the package insert.

We completed our review of this application and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 17-854/S-047." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

NDA 17-854/S-047

Page 2

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joyce Korvick
7/26/04 05:15:47 PM
for Dr. Robert Justice

Exhibit 4

NDA 17-854/S-047

Page 3

reglan[®] tablets

(metoclopramide tablets, USP)

PC4445D Rev. 02/04

Rx only

DESCRIPTION

For oral administration, reglan[®] tablets (metoclopramide tablets, USP) 10 mg are white, scored, capsule-shaped tablets engraved REGLAN on one side and SP 10 on the opposite side.

Each tablet contains:

Metoclopramide base 10 mg
(as the monohydrochloride monohydrate)

Inactive Ingredients

Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Stearic Acid.

reglan[®] tablets (metoclopramide tablets, USP) 5 mg are green, elliptical-shaped tablets engraved REGLAN 5 on one side and SP on the opposite side.

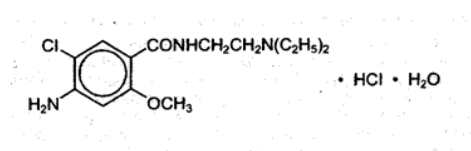
Each tablet contains:

Metoclopramide base 5 mg
(as the monohydrochloride monohydrate)

Inactive Ingredients

Corn starch, D&C Yellow 10 Aluminum Lake, FD&C Blue 1 Aluminum Lake, Lactose, Microcrystalline Cellulose, Silicon Dioxide, Stearic Acid.

Metoclopramide hydrochloride is a white crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Its molecular formula is $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$. Its molecular weight is 354.3.

**CLINICAL PHARMACOLOGY**

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

NDA 17-854/S-047

Page 4

Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any, effect on the motility of the colon or gallbladder.

In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5 mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like l-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions, although these are comparatively rare (see **WARNINGS**). Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with transient fluid retention.

The onset of pharmacological action of metoclopramide is 1 to 3 minutes following an intravenous dose, 10 to 15 minutes following intramuscular administration, and 30 to 60 minutes following an oral dose; pharmacological effects persist for 1 to 2 hours.

Pharmacokinetics

Metoclopramide is rapidly and well absorbed. Relative to an intravenous dose of 20 mg, the absolute oral bioavailability of metoclopramide is $80\% \pm 15.5\%$ as demonstrated in a crossover study of 18 subjects. Peak plasma concentrations occur at about 1 to 2 hr after a single oral dose. Similar time to peak is observed after individual doses at steady state.

In a single dose study of 12 subjects, the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5 to 6 hr. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hr. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide.

The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to the tissues.

NDA 17-854/S-047

Page 5

Renal impairment affects the clearance of metoclopramide. In a study with patients with varying degrees of renal impairment, a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance, and increase in elimination half-life. The kinetics of metoclopramide in the presence of renal impairment remained linear however. The reduction in clearance as a result of renal impairment suggests that adjustment downward of maintenance dosage should be done to avoid drug accumulation.

| Adult Pharmacokinetic Data | |
|-----------------------------------|--------------|
| Parameter | Value |
| Vd (L/kg) | ~ 3.5 |
| Plasma Protein Binding | ~ 30% |
| t _{1/2} (hr) | 5 to 6 |
| Oral Bioavailability | 80%±15.5% |

In pediatric patients, the pharmacodynamics of metoclopramide following oral and intravenous administration are highly variable and a concentration-effect relationship has not been established.

There are insufficient reliable data to conclude whether the pharmacokinetics of metoclopramide in adults and the pediatric population are similar. Although there are insufficient data to support the efficacy of metoclopramide in pediatric patients with symptomatic gastroesophageal reflux (GER) or cancer chemotherapy-related nausea and vomiting, its pharmacokinetics have been studied in these patient populations.

In an open-label study, six pediatric patients (age range, 3.5 weeks to 5.4 months) with GER received metoclopramide 0.15 mg/kg oral solution every 6 hours for 10 doses. The mean peak plasma concentration of metoclopramide after the tenth dose was 2-fold (56.8 µg/L) higher compared to that observed after the first dose (29 µg/L) indicating drug accumulation with repeated dosing. After the tenth dose, the mean time to reach peak concentrations (2.2 hr), half-life (4.1 hr), clearance (0.67 L/h/kg), and volume of distribution (4.4 L/kg) of metoclopramide were similar to those observed after the first dose. In the youngest patient (age, 3.5 weeks), metoclopramide half-life after the first and the tenth dose (23.1 and 10.3 hr, respectively) was significantly longer compared to other infants due to reduced clearance. This may be attributed to immature hepatic and renal systems at birth.

Single intravenous doses of metoclopramide 0.22 to 0.46 mg/kg (mean, 0.35 mg/kg) were administered over 5 minutes to 9 pediatric cancer patients receiving chemotherapy (mean age, 11.7 years; range, 7 to 14 yr) for prophylaxis of cytotoxic-induced vomiting. The metoclopramide plasma concentrations extrapolated to time zero ranged from 65 to 395 µg/L (mean, 152 µg/L). The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.4 hr (range, 1.7 to 8.3 hr), 0.56 L/h/kg (range, 0.12 to 1.20 L/h/kg), and 3.0 L/kg (range, 1.0 to 4.8 L/kg), respectively.

In another study, nine pediatric cancer patients (age range, 1 to 9 yr) received 4 to 5 intravenous infusions (over 30 minutes) of metoclopramide at a dose of 2 mg/kg to control emesis. After the last dose, the peak serum concentrations of metoclopramide ranged from 1060 to 5680 µg/L. The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.5 hr (range, 2.0 to 12.5 hr), 0.37 L/h/kg (range, 0.10 to 1.24 L/h/kg), and 1.93 L/kg (range, 0.95 to 5.50 L/kg), respectively.

NDA 17-854/S-047

Page 6

INDICATIONS AND USAGE

The use of reglan[®] tablets is recommended for adults only. Therapy should not exceed 12 weeks in duration.

Symptomatic Gastroesophageal Reflux

reglan[®] tablets are indicated as short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.

The principal effect of metoclopramide is on symptoms of postprandial and daytime heartburn with less observed effect on nocturnal symptoms. If symptoms are confined to particular situations, such as following the evening meal, use of metoclopramide as single doses prior to the provocative situation should be considered, rather than using the drug throughout the day. Healing of esophageal ulcers and erosions has been endoscopically demonstrated at the end of a 12-week trial using doses of 15 mg q.i.d. As there is no documented correlation between symptoms and healing of esophageal lesions, patients with documented lesions should be monitored endoscopically.

Diabetic Gastroparesis (Diabetic Gastric Stasis)

reglan[®] tablets (metoclopramide tablets, USP) is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartburn, persistent fullness after meals, and anorexia) appear to respond to reglan[®] within different time intervals. Significant relief of nausea occurs early and continues to improve over a three-week period. Relief of vomiting and anorexia may precede the relief of abdominal fullness by one week or more.

CONTRAINDICATIONS

Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine.

Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug.

Metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.

WARNINGS

Mental depression has occurred in patients with and without prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

NDA 17-854/S-047

Page 7

Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the usual adult dosages of 30 to 40 mg/day of metoclopramide. These usually are seen during the first 24 to 48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and adult patients less than 30 years of age and are even more frequent at higher doses. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, or dystonic reactions resembling tetanus. Rarely, dystonic reactions may present as stridor and dyspnea, possibly due to laryngospasm. If these symptoms should occur, inject 50 mg diphenhydramine hydrochloride intramuscularly, and they usually will subside. Benzotropine mesylate, 1 to 2 mg intramuscularly, may also be used to reverse these reactions.

Parkinsonian-like symptoms have occurred, more commonly within the first 6 months after beginning treatment with metoclopramide, but occasionally after longer periods. These symptoms generally subside within 2 to 3 months following discontinuance of metoclopramide. Patients with preexisting Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible.

There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.

Neuroleptic Malignant Syndrome (NMS)

There have been rare reports of an uncommon but potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) associated with metoclopramide. Clinical manifestations of NMS include hyperthermia, muscle rigidity, altered consciousness, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac arrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, malignant hyperthermia, drug fever and primary central nervous system (CNS) pathology.

NDA 17-854/S-047

Page 8

The management of NMS should include 1) immediate discontinuation of metoclopramide and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. Bromocriptine and dantrolene sodium have been used in treatment of NMS, but their effectiveness have not been established (see **ADVERSE REACTIONS**).

PRECAUTIONS

General

In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; hence, caution should be exercised when metoclopramide is used in patients with hypertension.

Because metoclopramide produces a transient increase in plasma aldosterone, certain patients, especially those with cirrhosis or congestive heart failure, may be at risk of developing fluid retention and volume overload. If these side effects occur at any time during metoclopramide therapy, the drug should be discontinued.

Adverse reactions, especially those involving the nervous system, may occur after stopping the use of reglan[®]. A small number of patients may experience a withdrawal period after stopping reglan[®] that could include dizziness, nervousness, and/or headaches.

Information for Patients

The use of reglan[®] is recommended for adults only. Metoclopramide may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be cautioned accordingly.

Drug Interactions

The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.

The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

Absorption of drugs from the stomach may be diminished (e.g., digoxin) by metoclopramide, whereas the rate and/or extent of absorption of drugs from the small bowel may be increased (e.g., acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

Gastroparesis (gastric stasis) may be responsible for poor diabetic control in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because the action of metoclopramide will influence the delivery of food to the intestines and thus the rate of absorption, insulin dosage or timing of dosage may require adjustment.

NDA 17-854/S-047

Page 9

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 77-week study was conducted in rats with oral doses up to about 40 times the maximum recommended human daily dose. Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

An Ames mutagenicity test performed on metoclopramide was negative.

Pregnancy Category B

Reproduction studies performed in rats, mice and rabbits by the I.V., I.M., S.C., and oral routes at maximum levels ranging from 12 to 250 times the human dose have demonstrated no impairment of fertility or significant harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established (see **OVERDOSAGE**).

Care should be exercised in administering metoclopramide to neonates since prolonged clearance may produce excessive serum concentrations (see **CLINICAL PHARMACOLOGY— Pharmacokinetics**). In addition, neonates have reduced levels of NADH-cytochrome b₅ reductase which, in combination with the aforementioned pharmacokinetic factors, make neonates more susceptible to methemoglobinemia (see **OVERDOSAGE**).

The safety profile of metoclopramide in adults cannot be extrapolated to pediatric patients. Dystonias and other extrapyramidal reactions associated with metoclopramide are more common in the pediatric population than in adults. (See **WARNINGS** and **ADVERSE REACTIONS—Extrapyramidal Reactions**.)

Geriatric Use

Clinical studies of reglan[®] did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects.

The risk of developing parkinsonian-like side effects increases with ascending dose. Geriatric patients should receive the lowest dose of reglan[®] that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving reglan[®], reglan[®] should generally be discontinued before initiating any specific anti-parkinsonian agents (see **WARNINGS** and **DOSAGE AND ADMINISTRATION – For the Relief**

NDA 17-854/S-047

Page 10

of Symptomatic Gastroesophageal Reflux).

The elderly may be at greater risk for tardive dyskinesia (see **WARNINGS – Tardive Dyskinesia**).

Sedation has been reported in reglan[®] users. Sedation may cause confusion and manifest as over-sedation in the elderly (see **CLINICAL PHARMACOLOGY, PRECAUTIONS – Information for Patients** and **ADVERSE REACTIONS – CNS Effects**).

reglan[®] is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION – USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT**).

For these reasons, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, concomitant disease, or other drug therapy in the elderly (see **DOSAGE AND ADMINISTRATION – For the Relief of Symptomatic Gastroesophageal Reflux** and **USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT**).

Other Special Populations

Patients with NADH-cytochrome b₅ reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended (see **OVERDOSAGE**).

ADVERSE REACTIONS

In general, the incidence of adverse reactions correlates with the dose and duration of metoclopramide administration. The following reactions have been reported, although in most instances, data do not permit an estimate of frequency:

CNS Effects

Restlessness, drowsiness, fatigue, and lassitude occur in approximately 10% of patients receiving the most commonly prescribed dosage of 10 mg q.i.d. (see **PRECAUTIONS**). Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation (see **WARNINGS**) occur less frequently. The incidence of drowsiness is greater at higher doses. There are isolated reports of convulsive seizures without clearcut relationship to metoclopramide. Rarely, hallucinations have been reported.

Extrapyramidal Reactions (EPS)

Acute dystonic reactions, the most common type of EPS associated with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30 to 40 mg of metoclopramide per day. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (tetanus-like reactions), and, rarely, stridor and dyspnea possibly due to laryngospasm; ordinarily these symptoms are readily reversed by diphenhydramine (see **WARNINGS**).

Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, mask-like facies (see **WARNINGS**).

Tardive dyskinesia most frequently is characterized by involuntary movements of the tongue, face, mouth, or jaw, and sometimes by involuntary movements of the trunk and/or extremities; movements may be

NDA 17-854/S-047

Page 11

choreoathetotic in appearance (see **WARNINGS**).

Motor restlessness (akathisia) may consist of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing, foot tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

Neuroleptic Malignant Syndrome

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported. This potentially fatal syndrome is comprised of the symptom complex of hyperthermia, altered consciousness, muscular rigidity, and autonomic dysfunction (see **WARNINGS**).

Endocrine Disturbances

Galactorrhea, amenorrhea, gynecomastia, impotence secondary to hyperprolactinemia (see **PRECAUTIONS**). Fluid retention secondary to transient elevation of aldosterone (see **CLINICAL PHARMACOLOGY**).

Cardiovascular

Hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention, acute congestive heart failure and possible AV block (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Gastrointestinal

Nausea and bowel disturbances, primarily diarrhea.

Hepatic

Rarely, cases of hepatotoxicity, characterized by such findings as jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

Renal

Urinary frequency and incontinence

Hematologic

A few cases of neutropenia, leukopenia, or agranulocytosis, generally without clearcut relationship to metoclopramide. Methemoglobinemia, in adults and especially with overdosage in neonates (see **OVERDOSAGE**). Sulfhemoglobinemia in adults.

Allergic Reactions

A few cases of rash, urticaria, or bronchospasm, especially in patients with a history of asthma. Rarely, angioneurotic edema, including glossal or laryngeal edema.

Miscellaneous

Visual disturbances. Porphyria.

OVERDOSAGE

Symptoms of overdosage may include drowsiness, disorientation and extrapyramidal reactions. Anticholinergic or antiparkinson drugs or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. Symptoms are self-limiting and usually disappear within 24 hours.

NDA 17-854/S-047

Page 12

Hemodialysis removes relatively little metoclopramide, probably because of the small amount of the drug in blood relative to tissues. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of drug. It is unlikely that dosage would need to be adjusted to compensate for losses through dialysis. Dialysis is not likely to be an effective method of drug removal in overdose situations.

Unintentional overdose due to misadministration has been reported in infants and children with the use of metoclopramide oral solution. While there was no consistent pattern to the reports associated with these overdoses, events included seizures, extrapyramidal reactions, and lethargy.

Methemoglobinemia has occurred in premature and full-term neonates who were given overdoses of metoclopramide (1 to 4 mg/kg/day orally, intramuscularly or intravenously for 1 to 3 or more days). Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal (see **PRECAUTIONS – Other Special Populations**).

DOSAGE AND ADMINISTRATION

Therapy with reglan[®] tablets should not exceed 12 weeks in duration.

For the Relief of Symptomatic Gastroesophageal Reflux

Administer from 10 mg to 15 mg reglan[®] (metoclopramide hydrochloride, USP) orally up to q.i.d. 30 minutes before each meal and at bedtime, depending upon symptoms being treated and clinical response (see **CLINICAL PHARMACOLOGY** and **INDICATIONS AND USAGE**). If symptoms occur only intermittently or at specific times of the day, use of metoclopramide in single doses up to 20 mg prior to the provoking situation may be preferred rather than continuous treatment. Occasionally, patients (such as elderly patients) who are more sensitive to the therapeutic or adverse effects of metoclopramide will require only 5 mg per dose.

Experience with esophageal erosions and ulcerations is limited, but healing has thus far been documented in one controlled trial using q.i.d. therapy at 15 mg/dose, and this regimen should be used when lesions are present, so long as it is tolerated (see **ADVERSE REACTIONS**). Because of the poor correlation between symptoms and endoscopic appearance of the esophagus, therapy directed at esophageal lesions is best guided by endoscopic evaluation.

Therapy longer than 12 weeks has not been evaluated and cannot be recommended.

For the Relief of Symptoms Associated with Diabetic Gastroparesis (Diabetic Gastric Stasis)

Administer 10 mg of metoclopramide 30 minutes before each meal and at bedtime for two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation.

The initial route of administration should be determined by the severity of the presenting symptoms. If only the earliest manifestations of diabetic gastric stasis are present, oral administration of reglan[®] may be initiated. However, if severe symptoms are present, therapy should begin with metoclopramide injection (consult labeling of the injection prior to initiating parenteral administration).

NDA 17-854/S-047

Page 13

Administration of metoclopramide injection up to 10 days may be required before symptoms subside, at which time oral administration may be instituted. Since diabetic gastric stasis is frequently recurrent, reglan[®] therapy should be reinstituted at the earliest manifestation.

USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 mL/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

See **OVERDOSAGE** section for information regarding dialysis.

Metoclopramide undergoes minimal hepatic metabolism, except for simple conjugation. Its safe use has been described in patients with advanced liver disease whose renal function was normal.

HOW SUPPLIED

Each white, capsule-shaped, scored reglan[®] tablet (metoclopramide tablets, USP) contains 10 mg metoclopramide base (as the monohydrochloride monohydrate). Available in:

Bottles of 100 tablets (NDC 0091-6701-63)

Bottles of 500 tablets (NDC 0091-6701-70)

Each green, elliptical-shaped reglan[®] tablet (metoclopramide tablets, USP) contains 5 mg metoclopramide base (as the monohydrochloride monohydrate). Available in:

Bottles of 100 tablets (NDC 0091-6705-63)

Dispense tablets in tight, light-resistant container.

Tablets should be stored at controlled room temperature, between 20°C and 25°C (68°F and 77°F).

SCHWARZ
P H A R M A
Milwaukee, WI 53201, USA

PC4445D

Rev. 02/04

Exhibit 5

5. Attached as Exhibits C and D are true and correct copies of letters from Teva to the FDA, dated July 20, 2009, and accompanying CBE Supplement. These materials include a true and correct copy of Teva's package insert for metoclopramide tablets as of July 20, 2009, which reflects all of the required language approved by the FDA on June 30, 2009.

6. Attached as Exhibit E is a true and correct copy of an excerpt from the National Drug Code Directory on the FDA's website, available at <http://www.accessdata.fda.gov/scripts/cder/ndc/results.cfm?searchfield=0093%2D2203&searchtype=NDCPackageCode&OrderBy=NDCPackageCode>. This excerpt indicates that Teva's National Drug Code for 10 mg metoclopramide is 0093-2203.

FURTHER, AFFIANT SAYETH NAUGHT.



SWORN TO and subscribed in my presence this 10th day of April, 2013.

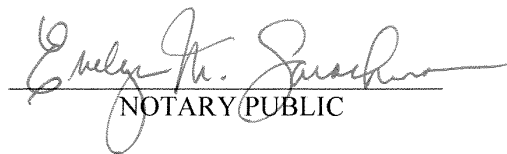
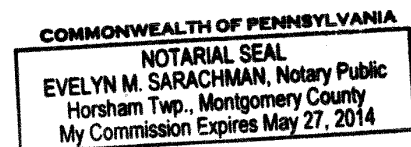
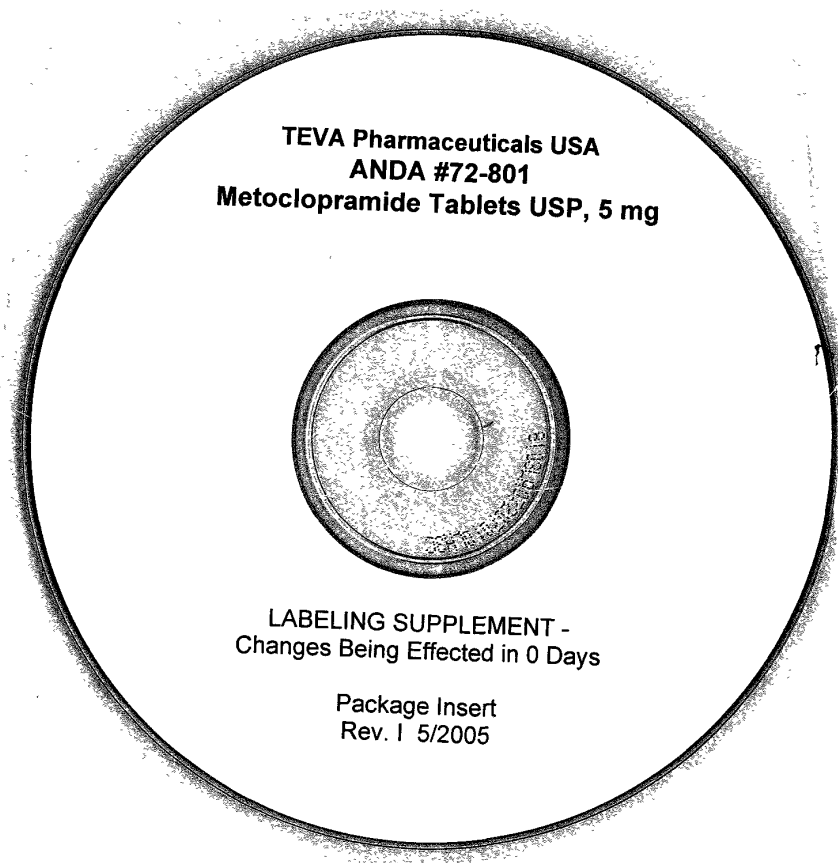

NOTARY PUBLIC

Exhibit A



| | | |
|---|--|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i> | | Form Approved: OMB No. 0910-0338 Expiration Date: August 31, 2005 See OMB Statement on page 2. |
| | | FOR FDA USE ONLY |
| | | APPLICATION NUMBER |
| APPLICANT INFORMATION | | |
| NAME OF APPLICANT TEVA Pharmaceuticals USA | DATE OF SUBMISSION June 24, 2005 | |
| TELEPHONE NO. (Include Area Code) (215) 591-3000 | FACSIMILE (FAX) Number (Include Area Code) (215) 591-8812 | |
| APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 1090 Horsham Road PO Box 1090 North Wales, PA 19454 | AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE | |
| PRODUCT DESCRIPTION | | |
| NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 72-801 | | |
| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) METOCLOPRAMIDE TABLETS, USP | PROPRIETARY NAME (trade name) IF ANY N/A | |
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Benzamide, 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy- | | CODE NAME (If any) N/A |
| DOSAGE FORM: TABLET | STRENGTHS: 5 mg | ROUTE OF ADMINISTRATION: ORAL |
| (PROPOSED) INDICATION(S) FOR USE: Symptomatic gastroesophageal reflux: indicated as short term (4 to 12 weeks) therapy for adults with symptomatic, documented reflux who fail to respond to conventional therapy. Diabetic gastroparesis (diabetic gastric stasis): indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. | | |
| APPLICATION INFORMATION | | |
| APPLICATION TYPE (check one) <input type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input checked="" type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601) | | |
| IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2) | | |
| IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION | | |
| Name of Drug REGLAN® Holder of Approved Application AH ROBINS COMPANY | | |
| TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER | | |
| IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____ | | |
| IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input checked="" type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA) | | |
| REASON FOR SUBMISSION SUPPLEMENT – Changes Being Effectuated in 0 Days | | |
| PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC) | | |
| NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC | | |
| ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. | | |
| N/A | | |
| Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) | | |
| N/A | | |

FORM FDA 356h (9/02)

PSC Media Arts. (301) 443-1090 EF

Page 1

| | | |
|---|--|--|
| This application contains the following items: (Check all that apply) | | |
| <input type="checkbox"/> | 1. Index | |
| <input checked="" type="checkbox"/> | 2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input checked="" type="checkbox"/> Final Printed Labeling | |
| <input type="checkbox"/> | 3. Summary (21 CFR 314.50 (c)) | |
| <input type="checkbox"/> | 4. Chemistry section | |
| <input type="checkbox"/> | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) | |
| <input type="checkbox"/> | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) | |
| <input type="checkbox"/> | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) | |
| <input type="checkbox"/> | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) | |
| <input type="checkbox"/> | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) | |
| <input type="checkbox"/> | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) | |
| <input type="checkbox"/> | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) | |
| <input type="checkbox"/> | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) | |
| <input type="checkbox"/> | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) | |
| <input type="checkbox"/> | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) | |
| <input type="checkbox"/> | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) | |
| <input type="checkbox"/> | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) | |
| <input type="checkbox"/> | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) | |
| <input type="checkbox"/> | 15. Establishment description (21 CFR Part 600, if applicable) | |
| <input type="checkbox"/> | 16. Debarment certification (FD&C Act 306 (k)(1)) | |
| <input type="checkbox"/> | 17. Field copy certification (21 CFR 314.50 (l)(3)) | |
| <input type="checkbox"/> | 18. User Fee Cover Sheet (Form FDA 3397) | |
| <input type="checkbox"/> | 19. Financial Information (21 CFR Part 54) | |
| <input checked="" type="checkbox"/> | 20. OTHER (Specify) <i>Electronic Cover Letter, 356h, and Package Insert</i> | |

CERTIFICATION

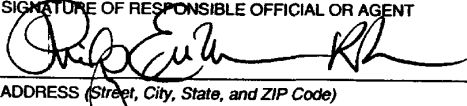
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| | | |
|--|---|---|
| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT  | TYPED NAME AND TITLE Philip Erickson, R.Ph. Senior Director, Regulatory Affairs | DATE: <i>6/24/05</i> |
| ADDRESS (Street, City, State, and ZIP Code) TEVA Pharmaceuticals USA 1090 Horsham Road, PO Box 1090, North Wales, PA 19454 | | Telephone Number (215) 591-3000 |

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

| | | |
|--|--|--|
| Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448 | Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852 | An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. |
|--|--|--|

FORM FDA 356h (9/02) PSC Media Arts (301) 443-1090 EF **Page 2**



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct Fax: (215) 591-8812
philip.erickson@tevausa.com

June 24, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING SUPPLEMENT

ANDA #72-801
METOCLOPRAMIDE TABLETS USP, 5 mg
SUPPLEMENT – CHANGES BEING EFFECTED IN 0 DAYS

Dear Mr. Buehler:

We submit herewith a supplement to the above-referenced ANDA in response to the insert revision for the Reference Listed Drug, approved on July 26, 2004. The revised package insert provided herein will be implemented immediately.

Enclosed please find a disk containing our revised package insert, Rev. I 5/2005 in PDF and Word formats, along with a comparison to the previous version of the package insert in PDF format. In accord with the Agency's Submission Guideline dated November 8, 1991, we draw your attention to the essentially identical supplement to the following application: ANDA #70-184 Metoclopramide Tablets USP, 10 mg.

This information is submitted for your review and approval. If there are any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

A handwritten signature in black ink, appearing to read "Philip Erickson". The signature is fluid and cursive, with a long horizontal line extending to the right.

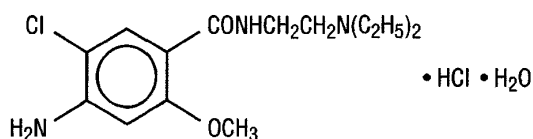
PE/dm
Enclosures

METOCLOPRAMIDE TABLETS USP

2204
2203

Rx only
DESCRIPTION

Metoclopramide hydrochloride is a white or practically white, crystalline, odorless or practically odorless powder. It is very soluble in water, freely soluble in alcohol, sparingly soluble in chloroform and practically insoluble in ether. Chemically, it is 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Its structural formula is as follows:



$C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$ M.W. 354.3

Each tablet for oral administration contains 5 mg or 10 mg metoclopramide (present as the hydrochloride).

Inactive Ingredients

Corn starch, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

CLINICAL PHARMACOLOGY

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum

and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any, effect on the motility of the colon or gallbladder.

In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5 mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like l-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions, although these are comparatively rare (see **WARNINGS**). Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with transient fluid retention.

The onset of pharmacological action of metoclopramide is 1 to 3 minutes following an intravenous dose, 10 to 15 minutes following intramuscular administration, and 30 to 60 minutes following an oral dose; pharmacological effects persist for 1 to 2 hours.

Pharmacokinetics

Metoclopramide is rapidly and well absorbed. Relative to an intravenous dose of 20 mg, the absolute oral bioavailability of metoclopramide is $80\% \pm 15.5\%$ as demonstrated in a crossover study of 18 subjects. Peak plasma concentrations occur at about 1 to 2 hr after a single oral dose. Similar time to peak is observed after individual doses at steady state.

In a single dose study of 12 subjects, the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5 to 6 hr. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hr. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide.

The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to the tissues.

Renal impairment affects the clearance of metoclopramide. In a study with patients with varying degrees of renal impairment, a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance, and increase in elimination half-life. The kinetics of metoclopramide in the presence of renal impairment remained linear however. The reduction in clearance as a result of renal impairment suggests that adjustment downward of maintenance dosage should be done to avoid drug accumulation.

Adult Pharmacokinetic Data

| Parameter | Value |
|------------------------|-------------|
| Vd (L/kg) | ~ 3.5 |
| Plasma Protein Binding | ~ 30% |
| t _{1/2} (hr) | 5 to 6 |
| Oral Bioavailability | 80% ± 15.5% |

In pediatric patients, the pharmacodynamics of metoclopramide following oral and intravenous administration are highly variable and a concentration-effect relationship has not been established.

There are insufficient reliable data to conclude whether the pharmacokinetics of metoclopramide in adults and the pediatric population are similar. Although there are insufficient data to support the efficacy of metoclopramide in pediatric patients with symptomatic gastroesophageal reflux (GER) or cancer chemotherapy-related nausea and vomiting, its pharmacokinetics have been studied in these patient populations.

In an open-label study, six pediatric patients (age range, 3.5 weeks to 5.4 months) with GER received metoclopramide 0.15 mg/kg oral solution every 6 hours for 10 doses. The mean peak plasma concentration of metoclopramide after the tenth dose was 2 fold (56.8 mcg/L) higher compared to that observed after the first dose (29 mcg/L) indicating drug accumulation with repeated dosing. After the tenth dose, the mean time to reach peak concentrations (2.2 hr), half-life (4.1 hr), clearance (0.67 L/h/kg), and volume of distribution (4.4 L/kg) of metoclopramide were similar to those observed after the first dose. In the youngest patient (age, 3.5 weeks), metoclopramide half-life after the first and the tenth dose (23.1 and 10.3 hr, respectively) was significantly longer compared to other infants due to reduced clearance. This may be attributed to immature hepatic and renal systems at birth.

Single intravenous doses of metoclopramide 0.22 to 0.46 mg/kg (mean, 0.35 mg/kg) were administered over 5 minutes to 9 pediatric cancer patients receiving chemotherapy (mean age, 11.7 years; range, 7 to 14 yr) for prophylaxis of cytotoxic-induced vomiting. The metoclopramide plasma concentrations extrapolated to time zero ranged from 65 to 395 mcg/L (mean, 152 mcg/L). The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.4 hr (range, 1.7 to 8.3 hr), 0.56 L/h/kg (range, 0.12 to 1.20 L/h/kg), and 3.0 L/kg (range, 1.0 to 4.8 L/kg), respectively.

In another study, nine pediatric cancer patients (age range, 1 to 9 yr) received 4 to 5 intravenous infusions (over 30 minutes) of metoclopramide at a dose of 2 mg/kg to control emesis. After the last dose, the peak serum concentrations of metoclopramide ranged from 1060 to 5680 mcg/L.

The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.5 hr (range, 2.0 to 12.5 hr), 0.37 L/h/kg (range, 0.10 to 1.24 L/h/kg), and 1.93 L/kg (range, 0.95 to 5.50 L/kg), respectively.

INDICATIONS AND USAGE

The use of metoclopramide tablets is recommended for adults only. Therapy should not exceed 12 weeks in duration.

Symptomatic Gastroesophageal Reflux

Metoclopramide tablets are indicated as short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.

The principal effect of metoclopramide is on symptoms of postprandial and daytime heartburn with less observed effect on nocturnal symptoms. If symptoms are confined to particular situations, such as following the evening meal, use of metoclopramide as single doses prior to the provocative situation should be considered, rather than using the drug throughout the day. Healing of esophageal ulcers and erosions has been endoscopically demonstrated at the end of a 12 week trial using doses of 15 mg q.i.d. As there is no documented correlation between symptoms and healing of esophageal lesions, patients with documented lesions should be monitored endoscopically.

Diabetic Gastroparesis (Diabetic Gastric Stasis)

Metoclopramide tablets are indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartburn, persistent fullness after meals, and anorexia) appear to respond to metoclopramide within different time intervals. Significant relief of nausea occurs early and continues to improve over a three-week period. Relief of vomiting and anorexia may precede the relief of abdominal fullness by one week or more.

CONTRAINDICATIONS

Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine.

Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug.

Metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.

WARNINGS

Mental depression has occurred in patients with and without prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the usual adult dosages of 30 to 40 mg/day of metoclopramide. These usually are seen during the first 24 to 48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and adult patients less than 30 years of age and are even more frequent at the higher doses. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, or dystonic reactions resembling tetanus. Rarely, dystonic reactions may present as stridor and dyspnea, possibly due to laryngospasm. If these symptoms should occur, inject 50 mg of diphenhydramine hydrochloride intramuscularly, and they usually will subside. Benztropine mesylate, 1 to 2 mg intramuscularly, may also be used to reverse these reactions.

Parkinsonian-like symptoms have occurred, more commonly within the first 6 months after beginning treatment with metoclopramide, but occasionally after longer periods. These symptoms generally subside within 2 to 3 months following discontinuance of metoclopramide. Patients with preexisting Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible.

There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.

Neuroleptic Malignant Syndrome (NMS)

There have been rare reports of an uncommon but potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) associated with metoclopramide. Clinical manifestations of NMS include hyperthermia, muscle rigidity, altered consciousness, and

evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac arrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, malignant hyperthermia, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of metoclopramide and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. Bromocriptine and dantrolene sodium have been used in treatment of NMS, but their effectiveness have not been established (see **ADVERSE REACTIONS**).

PRECAUTIONS

General

In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; hence, caution should be exercised when metoclopramide is used in patients with hypertension.

Because metoclopramide produces a transient increase in plasma aldosterone, certain patients, especially those with cirrhosis or congestive heart failure, may be at risk of developing fluid retention and volume overload. If these side effects occur at any time during metoclopramide therapy, the drug should be discontinued.

Adverse reactions, especially those involving the nervous system, may occur after stopping the use of metoclopramide. A small number of patients may experience a withdrawal period after stopping metoclopramide that could include dizziness, nervousness, and/or headaches.

Information for Patients

The use of metoclopramide is recommended for adults only. Metoclopramide may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be cautioned accordingly.

Drug Interactions

The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.

The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

Absorption of drugs from the stomach may be diminished (e.g., digoxin) by metoclopramide, whereas the rate and/or extent of absorption of drugs from the small bowel may be increased (e.g., acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

Gastroparesis (gastric stasis) may be responsible for poor diabetic control in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because the action of metoclopramide will influence the delivery of food to the intestines and thus the rate of absorption, insulin dosage or timing of dosage may require adjustment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 77 week study was conducted in rats with oral doses up to about 40 times the maximum recommended human daily dose. Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

An Ames mutagenicity test performed on metoclopramide was negative.

Pregnancy Category B

Reproduction studies performed in rats, mice and rabbits by the I.V., I.M., S.C., and oral routes at maximum levels ranging from 12 to 250 times the human dose have demonstrated no impairment of fertility or significant harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established (see **OVERDOSAGE**).

Care should be exercised in administering metoclopramide to neonates since prolonged clearance may produce excessive serum concentrations (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**). In addition, neonates have reduced levels of NADH-cytochrome b₅

reductase which, in combination with the aforementioned pharmacokinetic factors, make neonates more susceptible to methemoglobinemia (see **OVERDOSAGE**).

The safety profile of metoclopramide in adults cannot be extrapolated to pediatric patients. Dystonias and other extrapyramidal reactions associated with metoclopramide are more common in the pediatric population than in adults (see **WARNINGS** and **ADVERSE REACTIONS, Extrapyramidal Reactions**).

Geriatric Use

Clinical studies of metoclopramide did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects.

The risk of developing parkinsonian-like side effects increases with ascending dose. Geriatric patients should receive the lowest dose of metoclopramide that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving metoclopramide, metoclopramide should generally be discontinued before initiating any specific anti-parkinsonian agents (see **WARNINGS** and **DOSAGE AND ADMINISTRATION, For the Relief of Symptomatic Gastroesophageal Reflux**).

The elderly may be at greater risk for tardive dyskinesia (see **WARNINGS, Tardive Dyskinesia**).

Sedation has been reported in metoclopramide users. Sedation may cause confusion and manifest as over-sedation in the elderly (see **CLINICAL PHARMACOLOGY; PRECAUTIONS, Information for Patients; and ADVERSE REACTIONS, CNS Effects**).

Metoclopramide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION, Use in Patients with Renal or Hepatic Impairment**).

For these reasons, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, concomitant disease, or other drug therapy in the elderly (see **DOSAGE AND ADMINISTRATION, For the Relief of Symptomatic Gastroesophageal Reflux and Use in Patients with Renal or Hepatic Impairment**).

Other Special Populations

Patients with NADH-cytochrome b₅ reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended (see **OVERDOSAGE**).

ADVERSE REACTIONS

In general, the incidence of adverse reactions correlates with the dose and duration of metoclopramide administration. The following reactions have been reported, although in most instances, data do not permit an estimate of frequency:

CNS Effects

Restlessness, drowsiness, fatigue, and lassitude occur in approximately 10% of patients receiving the most commonly prescribed dosage of 10 mg q.i.d. (see **PRECAUTIONS**). Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation (see **WARNINGS**) occur less frequently. The incidence of drowsiness is greater at higher doses. There are isolated reports of convulsive seizures without clearcut relationship to metoclopramide. Rarely, hallucinations have been reported.

Extrapyramidal Reactions (EPS)

Acute dystonic reactions, the most common type of EPS associated with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30 to 40 mg of metoclopramide per day. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (tetanus-like reactions), and, rarely, stridor and dyspnea possibly due to laryngospasm; ordinarily these symptoms are readily reversed by diphenhydramine (see **WARNINGS**).

Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, mask-like facies (see **WARNINGS**).

Tardive dyskinesia most frequently is characterized by involuntary movements of the tongue, face, mouth, or jaw, and sometimes by involuntary movements of the trunk and/or extremities; movements may be choreoathetotic in appearance (see **WARNINGS**).

Motor restlessness (akathisia) may consist of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing, foot tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

Neuroleptic Malignant Syndrome

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported. This potentially fatal syndrome is comprised of the symptom complex of hyperthermia, altered consciousness, muscular rigidity, and autonomic dysfunction (see **WARNINGS**).

Endocrine Disturbances

Galactorrhea, amenorrhea, gynecomastia, impotence secondary to hyperprolactinemia (see **PRECAUTIONS**). Fluid retention secondary to transient elevation of aldosterone (see **CLINICAL PHARMACOLOGY**).

Cardiovascular

Hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention, acute congestive heart failure and possible AV block (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Gastrointestinal

Nausea and bowel disturbances, primarily diarrhea.

Hepatic

Rarely, cases of hepatotoxicity, characterized by such findings as jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

Renal

Urinary frequency and incontinence.

Hematologic

A few cases of neutropenia, leukopenia, or agranulocytosis, generally without clearcut relationship to metoclopramide. Methemoglobinemia, in adults and especially with overdosage in neonates (see **OVERDOSAGE**). Sulfhemoglobinemia in adults.

Allergic Reactions

A few cases of rash, urticaria, or bronchospasm, especially in patients with a history of asthma. Rarely, angioneurotic edema, including glossal or laryngeal edema.

Miscellaneous

Visual disturbances. Porphyrria.

OVERDOSAGE

Symptoms of overdosage may include drowsiness, disorientation, and extrapyramidal reactions. Anticholinergic or antiparkinson drugs or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. Symptoms are self-limiting and usually disappear within 24 hours.

Hemodialysis removes relatively little metoclopramide, probably because of the small amount of the drug in blood relative to tissues. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of drug. It is unlikely that dosage would need to be adjusted to compensate for losses through dialysis. Dialysis is not likely to be an effective method of drug removal in overdose situations.

Unintentional overdose due to misadministration has been reported in infants and children with the use of metoclopramide oral solution. While there was no consistent pattern to the reports associated with these overdoses, events included seizures, extrapyramidal reactions, and lethargy.

Methemoglobinemia has occurred in premature and full-term neonates who were given overdoses of metoclopramide (1 to 4 mg/kg/day orally, intramuscularly or intravenously for 1 to 3 or more days). Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal (see **PRECAUTIONS, Other Special Populations**).

DOSAGE AND ADMINISTRATION

Therapy with metoclopramide tablets should not exceed 12 weeks in duration.

For the Relief of Symptomatic Gastroesophageal Reflux

Administer from 10 mg to 15 mg of metoclopramide tablet, orally up to q.i.d. 30 minutes before each meal and at bedtime, depending upon symptoms being treated and clinical response (see **CLINICAL PHARMACOLOGY** and **INDICATIONS AND USAGE**). If symptoms occur only intermittently or at specific times of the day, use of metoclopramide in single doses up to 20 mg prior to the provoking situation may be preferred rather than continuous treatment. Occasionally, patients (such as elderly patients) who are more sensitive to the therapeutic or adverse effects of metoclopramide will require only 5 mg per dose.

Experience with esophageal erosions and ulcerations is limited, but healing has thus far been documented in one controlled trial using q.i.d. therapy at 15 mg/dose, and this regimen should be used when lesions are present, so long as it is tolerated (see **ADVERSE REACTIONS**). Because of the poor correlation between symptoms and endoscopic appearance of the esophagus, therapy directed at esophageal lesions is best guided by endoscopic evaluation.

Therapy longer than 12 weeks has not been evaluated and cannot be recommended.

For the Relief of Symptoms Associated with Diabetic Gastroparesis (Diabetic Gastric Stasis)

Administer 10 mg of metoclopramide 30 minutes before each meal and at bedtime for two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation.

The initial route of administration should be determined by the severity of the presenting symptoms. If only the earliest manifestations of diabetic gastric stasis are present, oral administration of metoclopramide may be initiated. However, if severe symptoms are present, therapy should begin with metoclopramide injection (consult labeling of the injection prior to initiating parenteral administration).

Administration of metoclopramide injection up to 10 days may be required before symptoms subside, at which time oral administration may be instituted. Since diabetic gastric stasis is frequently recurrent, metoclopramide therapy should be reinstituted at the earliest manifestation.

Use in Patients with Renal or Hepatic Impairment

Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 mL/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

See **OVERDOSAGE** section for information regarding dialysis.

Metoclopramide undergoes minimal hepatic metabolism, except for simple conjugation. Its safe use has been described in patients with advanced liver disease whose renal function was normal.

HOW SUPPLIED

Each white, round, unscored, debossed "BL/92", compressed metoclopramide tablet contains 5 mg metoclopramide (present as the hydrochloride). Available in bottles of 100 and 500.

Each white, round, scored, debossed "BL/93", compressed metoclopramide tablet contains 10 mg metoclopramide (present as the hydrochloride). Available in bottles of 100, 500 and 1000.

Dispense in a tight, light-resistant container.

This product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

Tablets should be stored at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. I 5/2005



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METOCLOPRAMIDE TABLETS, USP

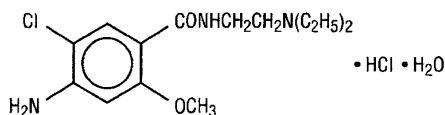
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Rx only**DESCRIPTION**

Metoclopramide hydrochloride is a white or practically white, crystalline, odorless or practically odorless powder. It is very soluble in water, freely soluble in alcohol, sparingly soluble in chloroform and practically insoluble in ether. Chemically, it is 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Its structural formula is as follows:

C₁₄H₂₂ClN₃O₂ HCl H₂O

M.W. 354.3

Each tablet for oral administration contains 5 mg or 10 mg metoclopramide (present as the hydrochloride).

Inactive Ingredients

Corn starch, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

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CLINICAL PHARMACOLOGY

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum

and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any, effect on the motility of the colon or gallbladder.

In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5 mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

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The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like L-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

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Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions, although these are comparatively rare (see **WARNINGS**). Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with transient fluid retention.

The onset of pharmacological action of metoclopramide is 1 to 3 minutes following an intravenous dose, 10 to 15 minutes following intramuscular administration, and 30 to 60 minutes following an oral dose; pharmacological effects persist for 1 to 2 hours.

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Pharmacokinetics

Metoclopramide is rapidly and well absorbed. Relative to an intravenous dose of 20 mg, the absolute oral bioavailability of metoclopramide is $80\% \pm 15.5\%$ as demonstrated in a crossover study of 18 subjects. Peak plasma concentrations occur at about 1 to 2 hr after a single oral dose. Similar time to peak is observed after individual doses at steady state.

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In a single dose study of 12 subjects, the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5 to 6 hr. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

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Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hr. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide.

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The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to the tissues.

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Adult Pharmacokinetic Data

| Parameter | Value |
|------------------------|-------------|
| Vd (L/kg) | ~ 3.5 |
| Plasma Protein Binding | ~ 30% |
| t _{1/2} (hr) | 5 to 6 |
| Oral Bioavailability | 80% = 15.5% |

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In an open-label study, six pediatric patients (age range, 3.5 weeks to 5.4 months) with GER received metoclopramide 0.15 mg/kg oral solution every 6 hours for 10 doses. The mean peak plasma concentration of metoclopramide after the tenth dose was 2 fold (56.8 mcg/L) higher compared to that observed after the first dose (29 mcg/L) indicating drug accumulation with repeated dosing. After the tenth dose, the mean time to reach peak concentrations (2.2 hr), half-life (4.1 hr), clearance (0.67 L/h/kg), and volume of distribution (4.4 L/kg) of metoclopramide were similar to those observed after the first dose. In the youngest patient (age, 3.5 weeks), metoclopramide half-life after the first and the tenth dose (23.1 and 10.3 hr, respectively) was significantly longer compared to other infants due to reduced clearance. This may be attributed to immature hepatic and renal systems at birth.

Single intravenous doses of metoclopramide 0.22 to 0.46 mg/kg (mean, 0.35 mg/kg) were administered over 5 minutes to 9 pediatric cancer patients receiving chemotherapy (mean age, 11.7 years; range, 7 to 14 yr) for prophylaxis of cytotoxic-induced vomiting. The metoclopramide plasma concentrations extrapolated to time zero ranged from 65 to 395 mcg/L (mean, 152 mcg/L). The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.4 hr (range, 1.7 to 8.3 hr), 0.56 L/h/kg (range, 0.12 to 1.20 L/h/kg), and 3.0 L/kg (range, 1.0 to 4.8 L/kg), respectively.

In another study, nine pediatric cancer patients (age range, 1 to 9 yr) received 4 to 5 intravenous infusions (over 30 minutes) of metoclopramide at a dose of 2 mg/kg to control emesis. After the last dose, the peak serum concentrations of metoclopramide ranged from 1060 to 5680 mcg/L.

The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.5 hr (range, 2.0 to 12.5 hr), 0.37 L/h/kg (range, 0.10 to 1.24 L/h/kg), and 1.93 L/kg (range, 0.95 to 5.50 L/kg), respectively.

INDICATIONS AND USAGE

The use of metoclopramide tablets is recommended for adults only. Therapy should not exceed 12 weeks in duration.

Symptomatic Gastroesophageal Reflux

Metoclopramide tablets are indicated as short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.

The principal effect of metoclopramide is on symptoms of postprandial and daytime heartburn with less observed effect on nocturnal symptoms. If symptoms are confined to particular situations, such as following the evening meal, use of metoclopramide as single doses prior to the provocative situation should be considered, rather than using the drug throughout the day. Healing of esophageal ulcers and erosions has been endoscopically demonstrated at the end of a 12 week trial using doses of 15 mg q.i.d. As there is no documented correlation between symptoms and healing of esophageal lesions, patients with documented lesions should be monitored endoscopically.

Diabetic Gastroparesis (Diabetic Gastric Stasis)

Metoclopramide tablets are indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartburn, persistent fullness after meals, and anorexia) appear to respond to metoclopramide within different time intervals. Significant relief of nausea occurs early and continues to improve over a three-week period. Relief of vomiting and anorexia may precede the relief of abdominal fullness by one week or more.

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CONTRAINDICATIONS

Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine.

Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug.

Metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.

WARNINGS

Mental depression has occurred in patients with and without prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the usual adult dosages of 30 to 40 mg/day of metoclopramide. These usually are seen during the first 24 to 48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and adult patients less than 30 years of age and are even more frequent at the higher doses. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, or dystonic reactions resembling tetanus. Rarely, dystonic reactions may present as stridor and dyspnea, possibly due to laryngospasm. If these symptoms should occur, inject 50 mg of diphenhydramine hydrochloride intramuscularly, and they usually will subside. Benztropine mesylate, 1 to 2 mg intramuscularly, may also be used to reverse these reactions.

Parkinsonian-like symptoms have occurred, more commonly within the first 6 months after beginning treatment with metoclopramide, but occasionally after longer periods. These symptoms generally subside within 2 to 3 months following discontinuance of metoclopramide. Patients with preexisting Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

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Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible.

There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.

Neuroleptic Malignant Syndrome (NMS)

There have been rare reports of an uncommon but potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) associated with metoclopramide. Clinical manifestations of NMS include hyperthermia, muscle rigidity, altered consciousness, and

evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac arrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, malignant hyperthermia, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of metoclopramide and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. Bromocriptine and dantrolene sodium have been used in treatment of NMS, but their effectiveness have not been established (see **ADVERSE REACTIONS**).

PRECAUTIONS

General

In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; hence, caution should be exercised when metoclopramide is used in patients with hypertension.

Because metoclopramide produces a transient increase in plasma aldosterone, certain patients, especially those with cirrhosis or congestive heart failure, may be at risk of developing fluid retention and volume overload. If these side effects occur at any time during metoclopramide therapy, the drug should be discontinued.

Adverse reactions, especially those involving the nervous system, may occur after stopping the use of metoclopramide. A small number of patients may experience a withdrawal period after stopping metoclopramide that could include dizziness, nervousness, and/or headaches.

Information for Patients

The use of metoclopramide is recommended for adults only. Metoclopramide may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be cautioned accordingly.

Drug Interactions

The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.

The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

Absorption of drugs from the stomach may be diminished (e.g., digoxin) by metoclopramide, whereas the rate and/or extent of absorption of drugs from the small bowel may be increased (e.g., acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

Gastroparesis (gastric stasis) may be responsible for poor diabetic control in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because the action of metoclopramide will influence the delivery of food to the intestines and thus the rate of absorption, insulin dosage or timing of dosage may require adjustment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 77 week study was conducted in rats with oral doses up to about 40 times the maximum recommended human daily dose. Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

An Ames mutagenicity test performed on metoclopramide was negative.

Pregnancy Category B

Reproduction studies performed in rats, mice and rabbits by the I.V., I.M., S.C., and oral routes at maximum levels ranging from 12 to 250 times the human dose have demonstrated no impairment of fertility or significant harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established (see **OVERDOSAGE**).

Care should be exercised in administering metoclopramide to neonates since prolonged clearance may produce excessive serum concentrations (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**). In addition, neonates have reduced levels of NADH-cytochrome b₅.

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dinucleotide-methemoglobin

reductase which, in combination with the aforementioned pharmacokinetic factors, make neonates more susceptible to methemoglobinemia (see **OVERDOSAGE**).

The safety profile of metoclopramide in adults cannot be extrapolated to pediatric patients. Dystonias and other extrapyramidal reactions associated with metoclopramide are more common in the pediatric population than in adults (see **WARNINGS** and **ADVERSE REACTIONS, Extrapyramidal Reactions**).

Geriatric Use

Clinical studies of metoclopramide did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects.

The risk of developing parkinsonian-like side effects increases with ascending dose. Geriatric patients should receive the lowest dose of metoclopramide that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving metoclopramide, metoclopramide should generally be discontinued before initiating any specific anti-parkinsonian agents (see **WARNINGS** and **DOSAGE AND ADMINISTRATION, For the Relief of Symptomatic Gastroesophageal Reflux**).

The elderly may be at greater risk for tardive dyskinesia (see **WARNINGS, Tardive Dyskinesia**).

Sedation has been reported in metoclopramide users. Sedation may cause confusion and manifest as over-sedation in the elderly (see **CLINICAL PHARMACOLOGY; PRECAUTIONS, Information for Patients; and ADVERSE REACTIONS, CNS Effects**).

Metoclopramide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION, Use in Patients with Renal or Hepatic Impairment**).

For these reasons, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, concomitant disease, or other drug therapy in the elderly (see **DOSAGE AND ADMINISTRATION, For the Relief of Symptomatic Gastroesophageal Reflux and Use in Patients with Renal or Hepatic Impairment**).

Other Special Populations

Patients with NADH-cytochrome b₅ reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended (see **OVERDOSAGE**).

ADVERSE REACTIONS

In general, the incidence of adverse reactions correlates with the dose and duration of metoclopramide administration. The following reactions have been reported, although in most instances, data do not permit an estimate of frequency:

CNS Effects

Restlessness, drowsiness, fatigue, and lassitude occur in approximately 10% of patients receiving the most commonly prescribed dosage of 10 mg q.i.d. (see **PRECAUTIONS**). Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation (see **WARNINGS**) occur less frequently. The incidence of drowsiness is greater at higher doses. There are isolated reports of convulsive seizures without clearcut relationship to metoclopramide. Rarely, hallucinations have been reported.

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Extrapyramidal Reactions (EPS)

Acute dystonic reactions, the most common type of EPS associated with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30 to 40 mg of metoclopramide per day. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (tetanus-like reactions), and, rarely, stridor and dyspnea possibly due to laryngospasm; ordinarily these symptoms are readily reversed by diphenhydramine (see **WARNINGS**).

Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, mask-like facies (see **WARNINGS**).

Tardive dyskinesia most frequently is characterized by involuntary movements of the tongue, face, mouth, or jaw, and sometimes by involuntary movements of the trunk and/or extremities; movements may be choreoathetotic in appearance (see **WARNINGS**).

Motor restlessness (akathisia) may consist of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing, foot tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

Neuroleptic Malignant Syndrome

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported. This potentially fatal syndrome is comprised of the symptom complex of hyperthermia, altered consciousness, muscular rigidity, and autonomic dysfunction (see **WARNINGS**).

Endocrine Disturbances

Galactorrhea, amenorrhea, gynecomastia, impotence secondary to hyperprolactinemia (see **PRECAUTIONS**). Fluid retention secondary to transient elevation of aldosterone (see **CLINICAL PHARMACOLOGY**).

Cardiovascular

Hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention, acute congestive heart failure, and possible AV block (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

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Gastrointestinal

Nausea and bowel disturbances, primarily diarrhea.

Hepatic

Rarely, cases of hepatotoxicity, characterized by such findings as jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

Renal

Urinary frequency and incontinence.

Hematologic

A few cases of neutropenia, leukopenia, or agranulocytosis, generally without clearcut relationship to metoclopramide. Methemoglobinemia, in adults and especially with overdosage in neonates (see **OVERDOSAGE**). Sulfhemoglobinemia in adults.

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Allergic Reactions

A few cases of rash, urticaria, or bronchospasm, especially in patients with a history of asthma. Rarely, angioneurotic edema, including glossal or laryngeal edema.

Miscellaneous

Visual disturbances. Porphyria.

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OVERDOSAGE

Symptoms of overdosage may include drowsiness, disorientation, and extrapyramidal reactions. Anticholinergic or antiparkinson drugs or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. Symptoms are self-limiting and usually disappear within 24 hours.

Hemodialysis removes relatively little metoclopramide, probably because of the small amount of the drug in blood relative to tissues. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of drug. It is unlikely that dosage would need to be adjusted to compensate for losses through dialysis. Dialysis is not likely to be an effective method of drug removal in overdose situations.

Unintentional overdose due to misadministration has been reported in infants and children with the use of metoclopramide oral solution. While there was no consistent pattern to the reports associated with these overdoses, events included seizures, extrapyramidal reactions, and lethargy.

Methemoglobinemia has occurred in premature and full-term neonates who were given overdoses of metoclopramide (1 to 4 mg/kg/day orally, intramuscularly or intravenously for 1 to 3 or more days). Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal (see **PRECAUTIONS, Other Special Populations**).

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DOSAGE AND ADMINISTRATION

Therapy with metoclopramide tablets should not exceed 12 weeks in duration.

For the Relief of Symptomatic Gastroesophageal Reflux

Administer from 10 mg to 15 mg of metoclopramide tablet, orally up to q.i.d. 30 minutes before each meal and at bedtime, depending upon symptoms being treated and clinical response (see **CLINICAL PHARMACOLOGY** and **INDICATIONS AND USAGE**). If symptoms occur only intermittently or at specific times of the day, use of metoclopramide in single doses up to 20 mg prior to the provoking situation may be preferred rather than continuous treatment. Occasionally, patients (such as elderly patients) who are more sensitive to the therapeutic or adverse effects of metoclopramide will require only 5 mg per dose.

Experience with esophageal erosions and ulcerations is limited, but healing has thus far been documented in one controlled trial using q.i.d. therapy at 15 mg/dose, and this regimen should be used when lesions are present, so long as it is tolerated (see **ADVERSE REACTIONS**). Because of the poor correlation between symptoms and endoscopic appearance of the esophagus, therapy directed at esophageal lesions is best guided by endoscopic evaluation.

Therapy longer than 12 weeks has not been evaluated and cannot be recommended.

For the Relief of Symptoms Associated with Diabetic Gastroparesis (Diabetic Gastric Stasis)

Administer 10 mg of metoclopramide 30 minutes before each meal and at bedtime for two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation.

The initial route of administration should be determined by the severity of the presenting symptoms. If only the earliest manifestations of diabetic gastric stasis are present, oral administration of metoclopramide may be initiated. However, if severe symptoms are present, therapy should begin with metoclopramide injection (consult labeling of the injection prior to initiating parenteral administration).

Administration of metoclopramide injection up to 10 days may be required before symptoms subside, at which time oral administration may be instituted. Since diabetic gastric stasis is frequently recurrent, metoclopramide therapy should be reinstituted at the earliest manifestation.

Use in Patients with Renal or Hepatic Impairment

Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 mL/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

See **OVERDOSAGE** section for information regarding dialysis.

Metoclopramide undergoes minimal hepatic metabolism, except for simple conjugation. Its safe use has been described in patients with advanced liver disease whose renal function was normal.

HOW SUPPLIED

Each white, round, unscored, debossed "BL/92", compressed metoclopramide tablet contains 5 mg metoclopramide (present as the hydrochloride). Available in bottles of 100 and 500.

Each white, round, scored, debossed "BL/93", compressed metoclopramide tablet contains 10 mg metoclopramide (present as the hydrochloride). Available in bottles of 100, 500 and 1000.

Dispense in a tight, light-resistant container.

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This product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

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Tablets should be stored at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

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Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. 1 5/2005

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Page 3: [1] Deleted TEVA 6/6/2005 9:35 AM

| Parameter | Value |
|------------------------|-------------|
| Vd (L/kg) | ~ 3.5 |
| Plasma Protein Binding | ~ |
| 30% | |
| t _{1/2} (hr) | 5 to 6 |
| Oral Bioavailability | 80% ± 15.5% |

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Pediatric Pharmacokinetic Studies

| Reference | Dose, Route | T _{1/2} (hr) | Cl (L/hr/kg) | Vd (L/kg) | C _{max} (mcg/L) |
|-----------|---|--------------------------|-----------------|-------------------------------------|--|
| 1. | 0.15 mg/kg oral soln, multiple dose | 4.1 ^{a, b} | 0.67 ± 0.14 | 4.4 ± 0.65 (Vd _{area}) | 1 st dose = 29 ± 2.3 10 th dose = 56.8 ± 10.5 |

Data presented as means ± SEM.

SEM not available.Kearns, GL, et al. *J Pediatric Gastroenterol Nutr* 7(6):823-829, 1988.

Exhibit B



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct Fax: (215) 591-8812
philip.erickson@tevausa.com

June 24, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING SUPPLEMENT

ANDA #70-184
METOCLOPRAMIDE TABLETS USP, 10 mg
SUPPLEMENT – CHANGES BEING EFFECTED IN 0 DAYS

Dear Mr. Buehler:

We submit herewith a supplement to the above-referenced ANDA in response to the insert revision for the Reference Listed Drug, approved on July 26, 2004. The revised package insert provided herein will be implemented immediately.

Enclosed please find a disk containing our revised package insert, Rev. I 5/2005 in PDF and Word formats, along with a comparison to the previous version of the package insert in PDF format. In accord with the Agency's Submission Guideline dated November 8, 1991, we draw your attention to the essentially identical supplement to the following application: ANDA #72-801 Metoclopramide Tablets USP, 5 mg.

This information is submitted for your review and approval. If there are any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

A handwritten signature in dark ink, appearing to read "Philip Erickson", followed by a horizontal line.

PE/dm
Enclosures

Exhibit C



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

July 20, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**SPECIAL SUPPLEMENT –
CHANGES BEING EFFECTED IN 0 DAYS**

ANDA #72-801
METOCLOPRAMIDE TABLETS USP, 5 mg
SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED IN 0 DAYS

Dear Mr. Buehler:

We submit herewith a Special Supplement – Changes Being Effectuated in 0 days to the above-referenced Abbreviated New Drug Application. Specifically, Teva's drug product labeling has been revised in accord with the most current labeling for the reference listed drug (RLD), Reglan® Tablets (NDA 17-854, approved on June 30, 2009). Pursuant to Section 505(o)(4) of the FDCA, the RLD labeling was revised to include new safety information pertaining to the risk of tardive dyskinesia. In addition, the RLD labeling now contains an Agency-approved Medication Guide, which has become a part of the RLD's Risk Evaluation and Mitigation Strategy (REMS).

Based on the aforementioned RLD updates, Teva's drug product labeling has been revised to include a revised package insert with new safety information and a new Medication Guide. Pursuant to 21 CFR 208.24(b), Teva Pharmaceuticals USA hereby states that a sufficient number of Medication Guides will be affixed to each bottle provided to the authorized dispensers such that the dispenser can provide a Medication Guide to each patient receiving the drug product. Specifically, 4 Medication Guides will be affixed to the 100 count bottle and 17 Medication Guides will be affixed to the 500 count bottle. Furthermore, in accord with 21 CFR 208.24(d), Teva Pharmaceuticals USA's container labeling has been revised to include a statement, in a prominent and conspicuous manner, instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed.

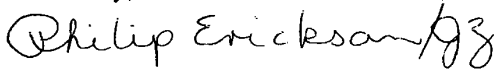
ANDA #72-801
METOCLOPRAMIDE TABLETS USP, 5 mg
SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED IN 0 DAYS
Page 2 of 2

Enclosed herein on 1 CD-ROM, please find the following:

- Revised Final Print Package Insert (Rev. J 7/2009) in Word, PDF, and SPL formats, with a PDF comparison to Teva's previously submitted insert (Rev. I 5/2005)
- New Final Print Medication Guide (Iss. 7/2009) in Word, PDF, and SPL formats, with a PDF comparison to RLD's Agency-approved Medication Guide (Revised June 2009).
- Revised Container Labels for the 100 count (Rev. E 7/2009) and 500 count (Rev. F 7/2009) bottles in Word and PDF formats, with a PDF comparison to Teva's previously submitted container labels

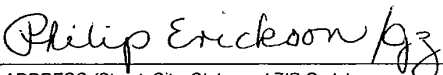
The information is submitted for your review and approval. If there are any questions, please do not hesitate to contact me by telephone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

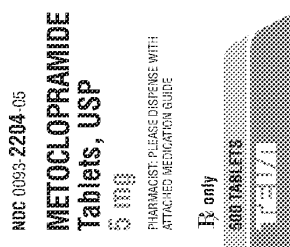
A handwritten signature in cursive script that reads "Philip Erickson" followed by a stylized flourish.

PE/sa
Enclosures

| | | |
|---|--|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i> | | Form Approved: OMB No. 0910-0430 Expiration Date: April 30, 2009 See OMB Statement on page 2. |
| | | FOR FDA USE ONLY |
| | | APPLICATION NUMBER |
| APPLICANT INFORMATION | | |
| NAME OF APPLICANT TEVA Pharmaceuticals USA | DATE OF SUBMISSION July 20, 2009 | |
| TELEPHONE NO. (Include Area Code) (215) 591-3000 | FACSIMILE (FAX) Number (Include Area Code) (215) 591-8812 | |
| APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 1090 Horsham Road PO Box 1090 North Wales, PA 19454 | AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE | |
| PRODUCT DESCRIPTION | | |
| NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 72-801 | | |
| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) METOCLOPRAMIDE TABLETS, USP | PROPRIETARY NAME (trade name) IF ANY N/A | |
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate | CODE NAME (If any) N/A | |
| DOSAGE FORM: TABLET | STRENGTHS: 5 mg | ROUTE OF ADMINISTRATION: ORAL |
| (PROPOSED) INDICATION(S) FOR USE: Symptomatic gastroesophageal reflux: indicated as short term (4 to 12 weeks) therapy for adults with symptomatic, documented reflux who fail to respond to conventional therapy. Diabetic gastroparesis (diabetic gastric stasis): indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. | | |
| APPLICATION DESCRIPTION | | |
| APPLICATION TYPE (check one) <input type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input checked="" type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601) | | |
| IF AN NDA, IDENTIFY THE APPROPRIATE TYPE: <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2) | | |
| IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION | | |
| Name of Drug REGLAN® Holder of Approved Application ALAVEN PHARM | | |
| TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER | | |
| IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____ | | |
| IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input checked="" type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA) | | |
| REASON FOR SUBMISSION SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED IN 0 DAYS | | |
| PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC) | | |
| NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC | | |
| ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. N/A | | |
| Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) N/A | | |

| | | |
|---|--|---|
| This application contains the following items: (Check all that apply) | | |
| <input type="checkbox"/> | 1. Index | |
| <input checked="" type="checkbox"/> | 2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input checked="" type="checkbox"/> Final Printed Labeling | |
| <input type="checkbox"/> | 3. Summary (21 CFR 314.50 (c)) | |
| <input type="checkbox"/> | 4. Chemistry section | |
| <input type="checkbox"/> | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) | |
| <input type="checkbox"/> | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) | |
| <input type="checkbox"/> | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) | |
| <input type="checkbox"/> | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) | |
| <input type="checkbox"/> | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) | |
| <input type="checkbox"/> | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) | |
| <input type="checkbox"/> | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) | |
| <input type="checkbox"/> | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) | |
| <input type="checkbox"/> | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) | |
| <input type="checkbox"/> | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) | |
| <input type="checkbox"/> | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) | |
| <input type="checkbox"/> | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) | |
| <input type="checkbox"/> | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) | |
| <input type="checkbox"/> | 15. Establishment description (21 CFR Part 600, if applicable) | |
| <input type="checkbox"/> | 16. Debarment certification (FD&C Act 306 (k)(1)) | |
| <input type="checkbox"/> | 17. Field copy certification (21 CFR 314.50 (l)(3)) | |
| <input type="checkbox"/> | 18. User Fee Cover Sheet (Form FDA 3397) | |
| <input type="checkbox"/> | 19. Financial Information (21 CFR Part 54) | |
| <input checked="" type="checkbox"/> | 20. OTHER (Specify) 1 CD-ROM with labeling, 356h, and cover letter | |
| CERTIFICATION <p>I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:</p> <ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202. 5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81. 7. Local, state and Federal environmental impact laws. <p>If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p>Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p> | | |
| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | | DATE: |
|  | | Philip Erickson, R.Ph. Senior Director, Regulatory Affairs 7/20/09 |
| ADDRESS (Street, City, State, and ZIP Code) | | Telephone Number |
| TEVA Pharmaceuticals USA 1090 Horsham Road, PO Box 1090, North Wales, PA 19454 | | (215) 591-3000 |
| <p>Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> | | |
| Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266 | | Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448 |
| An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. | | |





Each tablet contains 5 mg metoclopramide (present as the hydrochloride).

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container.

PROTECT FROM LIGHT.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

0093-2204-05



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METOCLOPRAMIDE TABLETS USP – TEVA – CONTAINER LABEL

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Main Panel: **NDC 0093-2204-01**

METOCLOPRAMIDE Tablets, USP

5 mg

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PHARMACIST: PLEASE DISPENSE WITH ATTACHED MEDICATION
GUIDE

Rx only

Deleted: Each tablet contains.¶
Metoclopramide 5 mg¶
(present as the hydrochloride).¶
¶

100 TABLETS

TEVA

Side Panel: ~~Each tablet contains 5 mg metoclopramide (present as the hydrochloride).~~

Deleted: For dosage and other

Usual Dosage: See package insert for full prescribing information.

Deleted: , see accompanying
product literature

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container.

PROTECT FROM LIGHT.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF
CHILDREN.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. ~~E~~ 7/2009

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METOCLOPRAMIDE TABLETS USP – TEVA – CONTAINER LABEL

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Main Panel: NDC 0093-2204-05

METOCLOPRAMIDE Tablets, USP

5 mg

PHARMACIST: PLEASE DISPENSE WITH ATTACHED MEDICATION GUIDE

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Each tablet contains:¶
Metoclopramide . . . 5 mg¶
(present as the hydrochloride).¶

Rx only

500 TABLETS

TEVA

Side Panel: Each tablet contains 5 mg metoclopramide (present as the hydrochloride).

Deleted: For dosage and other

Usual Dosage: See package insert for full prescribing information.

Deleted: , see accompanying product literature

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container.

PROTECT FROM LIGHT.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. F 7/2009

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METOCLOPRAMIDE TABLETS USP – TEVA – CONTAINER LABEL

Main Panel: **NDC 0093-2204-01**

METOCLOPRAMIDE Tablets, USP

5 mg

PHARMACIST: PLEASE DISPENSE WITH ATTACHED MEDICATION
GUIDE

Rx only

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TEVA

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Rev. E 7/2009

METOCLOPRAMIDE TABLETS USP – TEVA – CONTAINER LABEL

Main Panel: **NDC 0093-2204-05**

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5 mg

PHARMACIST: PLEASE DISPENSE WITH ATTACHED MEDICATION
GUIDE

Rx only

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TEVA

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Usual Dosage: See package insert for full prescribing information.

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Rev. F 7/2009



Administrative Offices:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.

Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141

Direct FAX: (215) 591-8812

philip.erickson@tevausa.com

July 20, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**SPECIAL SUPPLEMENT –
CHANGES BEING EFFECTED IN 0 DAYS**

ANDA #72-801

METOCLOPRAMIDE TABLETS USP, 5 mg

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED IN 0 DAYS

Dear Mr. Buehler:

We submit herewith a Special Supplement – Changes Being Effected in 0 days to the above-referenced Abbreviated New Drug Application. Specifically, Teva's drug product labeling has been revised in accord with the most current labeling for the reference listed drug (RLD), Reglan® Tablets (NDA 17-854, approved on June 30, 2009). Pursuant to Section 505(o)(4) of the FDCA, the RLD labeling was revised to include new safety information pertaining to the risk of tardive dyskinesia. In addition, the RLD labeling now contains an Agency-approved Medication Guide, which has become a part of the RLD's Risk Evaluation and Mitigation Strategy (REMS).

Based on the aforementioned RLD updates, Teva's drug product labeling has been revised to include a revised package insert with new safety information and a new Medication Guide. Pursuant to 21 CFR 208.24(b), Teva Pharmaceuticals USA hereby states that a sufficient number of Medication Guides will be affixed to each bottle provided to the authorized dispensers such that the dispenser can provide a Medication Guide to each patient receiving the drug product. Specifically, 4 Medication Guides will be affixed to the 100 count bottle and 17 Medication Guides will be affixed to the 500 count bottle. Furthermore, in accord with 21 CFR 208.24(d), Teva Pharmaceuticals USA's container labeling has been revised to include a statement, in a prominent and conspicuous manner, instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed.

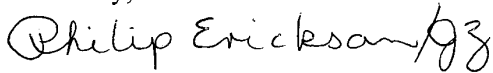
ANDA #72-801
METOCLOPRAMIDE TABLETS USP, 5 mg
SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED IN 0 DAYS
Page 2 of 2

Enclosed herein on 1 CD-ROM, please find the following:

- Revised Final Print Package Insert (Rev. J 7/2009) in Word, PDF, and SPL formats, with a PDF comparison to Teva's previously submitted insert (Rev. I 5/2005)
- New Final Print Medication Guide (Iss. 7/2009) in Word, PDF, and SPL formats, with a PDF comparison to RLD's Agency-approved Medication Guide (Revised June 2009).
- Revised Container Labels for the 100 count (Rev. E 7/2009) and 500 count (Rev. F 7/2009) bottles in Word and PDF formats, with a PDF comparison to Teva's previously submitted container labels

The information is submitted for your review and approval. If there are any questions, please do not hesitate to contact me by telephone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

A handwritten signature in black ink that reads "Philip Erickson" followed by a stylized flourish or initials.

PE/sa

Enclosures

Medication Guide

METOCLOPRAMIDE TABLETS, USP

Rx only

Read the Medication Guide that comes with metoclopramide tablets, USP before you start taking them and each time you get a refill. There may be new information. If you take another product that contains metoclopramide (such as metoclopramide injection, metoclopramide orally disintegrating tablets, or metoclopramide oral syrup), you should read the Medication Guide that comes with that product. Some of the information may be different. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about metoclopramide tablets, USP?

Metoclopramide tablets, USP can cause serious side effects, including:

Abnormal muscle movements called tardive dyskinesia (TD). These movements happen mostly in the face muscles. You can not control these movements. They may not go away even after stopping metoclopramide tablets, USP. There is no treatment for TD, but symptoms may lessen or go away over time after you stop taking metoclopramide tablets, USP.

Your chances for getting TD go up:

- the longer you take metoclopramide tablets, USP and the more metoclopramide tablets, USP you take. You should not take metoclopramide tablets, USP for more than 12 weeks.
- if you are older, especially if you are a woman
- if you have diabetes

It is not possible for your doctor to know if **you** will get TD if you take metoclopramide tablets, USP.

Call your doctor right away if you get movements you can not stop or control, such as:

- lip smacking, chewing, or puckering up your mouth
- frowning or scowling
- sticking out your tongue
- blinking and moving your eyes
- shaking of your arms and legs

See the section "**What are the possible side effects of metoclopramide tablets, USP?**" for more information about side effects.

What are metoclopramide tablets, USP?

Metoclopramide tablets, USP are a prescription medicine used:

- in adults for 4 to 12 weeks to relieve heartburn symptoms with gastroesophageal reflux disease (GERD) when certain other treatments do not work. Metoclopramide tablets, USP relieve daytime heartburn and heartburn after meals. They also help ulcers in the esophagus to heal.
- to relieve symptoms of slow stomach emptying in people with diabetes. Metoclopramide tablets, USP help treat symptoms such as nausea, vomiting, heartburn, feeling full long after a meal, and loss of appetite. Not all these symptoms get better at the same time.

It is not known if metoclopramide tablets, USP are safe and work in children.

Who should not take metoclopramide tablets, USP?

Do not take metoclopramide tablets, USP if you:

- have stomach or intestine problems that could get worse with metoclopramide tablets, USP, such as bleeding, blockage or a tear in the stomach or bowel wall
- have an adrenal gland tumor called a pheochromocytoma
- are allergic to metoclopramide tablets, USP or anything in them. See the end of this Medication Guide for a list of ingredients in metoclopramide tablets, USP.
- take medicines that can cause uncontrolled movements, such as medicines for mental illness
- have seizures

What should I tell my doctor before taking metoclopramide tablets, USP?

Tell your doctor about all your medical conditions, including if you have:

- depression
- Parkinson's disease
- high blood pressure
- kidney problems. Your doctor may start with a lower dose.
- liver problems or heart failure. Metoclopramide tablets, USP may cause your body to hold fluids.
- diabetes. Your dose of insulin may need to be changed.
- breast cancer
- you are pregnant or plan to become pregnant. It is not known if metoclopramide tablets, USP will harm your unborn baby.
- you are breast-feeding. Metoclopramide can pass into breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you take metoclopramide tablets, USP.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Metoclopramide tablets, USP and some other medicines may interact with each other and may not work as well, or cause possible side effects. Do not start any new medicines while taking metoclopramide tablets, USP until you talk with your doctor.

Especially tell your doctor if you take:

- another medicine that contains metoclopramide, such as metoclopramide orally disintegrating tablets, or metoclopramide oral syrup
- a blood pressure medicine
- a medicine for depression, especially a Monoamine Oxidase Inhibitor (MAOI)
- insulin
- a medicine that can make you sleepy, such as anti-anxiety medicine, sleep medicines, and narcotics.

If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.
Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take metoclopramide tablets, USP?

- Metoclopramide tablets, USP come as a tablet you take by mouth.
- Take metoclopramide tablets, USP exactly as your doctor tells you. Do not change your dose unless your doctor tells you.
- You should not take metoclopramide tablets, USP for more than 12 weeks.
- If you take too many metoclopramide tablets, USP, call your doctor or Poison Control Center right away.

What should I avoid while taking metoclopramide tablets, USP?

- Do not drink alcohol while taking metoclopramide tablets, USP. Alcohol may make some side effects of metoclopramide tablets, USP worse, such as feeling sleepy.
- Do not drive, work with machines, or do dangerous tasks until you know how metoclopramide tablets, USP affect you. Metoclopramide tablets, USP may cause sleepiness.

What are the possible side effects of metoclopramide tablets, USP?

Metoclopramide tablets, USP can cause serious side effects, including:

- **Abnormal muscle movements.** See "What is the most important information I need to know about metoclopramide tablets, USP?"
- **Uncontrolled spasms of your face and neck muscles, or muscles of your body, arms, and legs (dystonia).** These muscle spasms can cause abnormal movements and body positions. These spasms usually start within the first 2 days of treatment. These spasms happen more often in children and adults under age 30.
- **Depression, thoughts about suicide, and suicide.** Some people who take metoclopramide tablets, USP become depressed. You may have thoughts about hurting or killing yourself. Some people who take metoclopramide tablets, USP have ended their own lives (suicide).
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a very rare but very serious condition that can happen with metoclopramide tablets, USP. NMS can cause death and must be treated in a hospital. Symptoms of NMS include: high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating.
- **Parkinsonism.** Symptoms include slight shaking, body stiffness, trouble moving or keeping your balance. If you already have Parkinson's disease, your symptoms may become worse while you are receiving metoclopramide tablets, USP.

Call your doctor and get medical help right away if you:

- feel depressed or have thoughts about hurting or killing yourself
- have high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating

- have muscle movements you cannot stop or control
- have muscle movements that are new or unusual

Common side effects of metoclopramide tablets, USP include:

- feeling restless, sleepy, tired, dizzy, or exhausted
- headache
- confusion
- trouble sleeping

You may have more side effects the longer you take metoclopramide tablets, USP and the more metoclopramide tablets, USP you take.

You may still have side effects after stopping metoclopramide tablets, USP. You may have symptoms from stopping (withdrawal) metoclopramide tablets, USP such as headaches, and feeling dizzy or nervous.

Tell your doctor about any side effects that bother you or do not go away. These are not all the possible side effects of metoclopramide tablets, USP.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store metoclopramide tablets, USP?

- Keep metoclopramide tablets, USP at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep metoclopramide tablets, USP in the bottle they come in. Keep the bottle closed tightly.

Keep metoclopramide tablets, USP and all medicines out of the reach of children.

General information about metoclopramide tablets, USP

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use metoclopramide tablets, USP for a condition for which they were not prescribed. Do not give metoclopramide tablets, USP to other people, even if they have the same symptoms that you have. They may harm them.

This Medication Guide summarizes the most important information about metoclopramide tablets, USP. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about metoclopramide tablets, USP that is written for health professionals. For more information, call 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in metoclopramide tablets, USP?

Active ingredient: metoclopramide

Inactive ingredients: corn starch, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate

This Medication Guide has been approved by the U.S. Food and Drug Administration.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 7/2009

Medication Guide
METOCLOPRAMIDE TABLETS, USP

Read only

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Inactive ingredients: corn starch, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate

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TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 7/2009

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Medication Guide

METOCLOPRAMIDE TABLETS, USP

Rx only

Read the Medication Guide that comes with metoclopramide tablets, USP before you start taking them and each time you get a refill. There may be new information. If you take another product that contains metoclopramide (such as metoclopramide injection, metoclopramide orally disintegrating tablets, or metoclopramide oral syrup), you should read the Medication Guide that comes with that product. Some of the information may be different. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about metoclopramide tablets, USP?

Metoclopramide tablets, USP can cause serious side effects, including:

Abnormal muscle movements called tardive dyskinesia (TD). These movements happen mostly in the face muscles. You can not control these movements. They may not go away even after stopping metoclopramide tablets, USP. There is no treatment for TD, but symptoms may lessen or go away over time after you stop taking metoclopramide tablets, USP.

Your chances for getting TD go up:

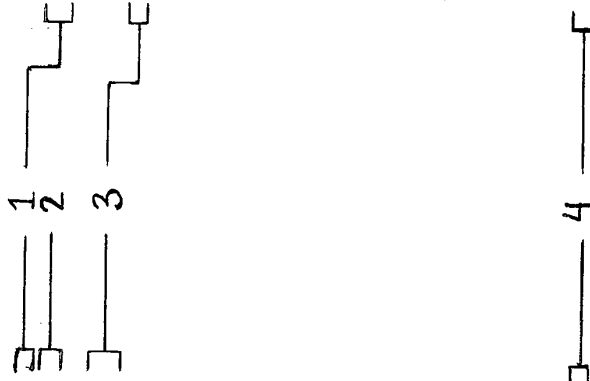
- the longer you take metoclopramide tablets, USP and the more metoclopramide tablets, USP you take. You should not take metoclopramide tablets, USP for more than 12 weeks.
- if you are older, especially if you are a woman
- if you have diabetes

It is not possible for your doctor to know if you will get TD if you take metoclopramide tablets, USP.

Call your doctor right away if you get movements you can not stop or control, such as:

- lip smacking, chewing, or puckering up your mouth
- frowning or scowling
- sticking out your tongue
- blinking and moving your eyes
- shaking of your arms and legs

See the section "What are the possible side effects of metoclopramide tablets, USP?" for more information about side effects.



Medication Guide

REGLAN (REG-lan) Tablets (metoclopramide tablets)

Read the Medication Guide that comes with REGLAN before you start taking it and each time you get a refill. There may be new information. If you take another product that contains metoclopramide (such as REGLAN injection, REGLAN ODT, or metoclopramide oral syrup), you should read the Medication Guide that comes with that product. Some of the information may be different. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about REGLAN?

REGLAN can cause serious side effects, including:

Abnormal muscle movements called tardive dyskinesia (TD). These movements happen mostly in the face muscles. You can not control these movements. They may not go away even after stopping REGLAN. There is no treatment for TD, but symptoms may lessen or go away over time after you stop taking REGLAN.

Your chances for getting TD go up:

- the longer you take REGLAN and the more REGLAN you take. You should not take REGLAN for more than 12 weeks.
- if you are older, especially if you are a woman
- if you have diabetes

It is not possible for your doctor to know if you will get TD if you take REGLAN.

Call your doctor right away if you get movements you can not stop or control, such as:

- lip smacking, chewing, or puckering up your mouth
- frowning or scowling
- sticking out your tongue
- blinking and moving your eyes
- shaking of your arms and legs

See the section "What are the possible side effects of REGLAN?" for more information about side effects.

1. "REGLAN" is replaced with "metoclopramide tablets, USP" when product name is mentioned and with "metoclopramide" when chemical name is mentioned throughout proposed medication guide to comply with Teva format.
2. "Rx only" appears below product name in the proposed medication guide to comply with Teva format.
3. "ODT" is replaced with "orally disintegrating tablets" throughout proposed medication guide to comply with Teva format.
4. "What are the possible side effects of REGLAN?" is replaced with "What are the possible side effects of metoclopramide tablets, USP?" in proposed medication guide to comply with Teva format.



What are metoclopramide tablets, USP?

Metoclopramide tablets, USP are a prescription medicine used:

- in adults for 4 to 12 weeks to relieve heartburn symptoms with gastroesophageal reflux disease (GERD) when certain other treatments do not work. Metoclopramide tablets, USP relieve daytime heartburn and heartburn after meals. They also help ulcers in the esophagus to heal.
- to relieve symptoms of slow stomach emptying in people with diabetes. Metoclopramide tablets, USP help treat symptoms such as nausea, vomiting, heartburn, feeling full long after a meal, and loss of appetite. Not all these symptoms get better at the same time.

It is not known if metoclopramide tablets, USP are safe and work in children.

Who should not take metoclopramide tablets, USP?

Do not take metoclopramide tablets, USP if you:

- have stomach or intestine problems that could get worse with metoclopramide tablets, USP, such as bleeding, blockage or a tear in the stomach or bowel wall
- have an adrenal gland tumor called a pheochromocytoma
- are allergic to metoclopramide tablets, USP or anything in them. See the end of this Medication Guide for a list of ingredients in metoclopramide tablets, USP.
- take medicines that can cause uncontrolled movements, such as medicines for mental illness
- have seizures

What should I tell my doctor before taking metoclopramide tablets, USP?

Tell your doctor about all your medical conditions, including if you have:

- depression
- Parkinson's disease
- high blood pressure
- kidney problems. Your doctor may start with a lower dose.
- liver problems or heart failure. Metoclopramide tablets, USP may cause your body to hold fluids.
- diabetes. Your dose of insulin may need to be changed.
- breast cancer
- you are pregnant or plan to become pregnant. It is not known if metoclopramide will harm your unborn baby.
- you are breast-feeding. Metoclopramide can pass into breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you take metoclopramide tablets, USP.

ALAVEN PHARMACEUTICAL

What is REGLAN?

REGLAN is a prescription medicine used:

- in adults for 4 to 12 weeks to relieve heartburn symptoms with gastroesophageal reflux disease (GERD) when certain other treatments do not work. REGLAN relieves daytime heartburn and heartburn after meals. It also helps ulcers in the esophagus to heal.
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- have an adrenal gland tumor called a pheochromocytoma
- are allergic to REGLAN or anything in it. See the end of this Medication Guide for a list of ingredients in REGLAN.
- take medicines that can cause uncontrolled movements, such as medicines for mental illness
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- liver problems or heart failure. REGLAN may cause your body to hold fluids.
- diabetes. Your dose of insulin may need to be changed.
- breast cancer
- you are pregnant or plan to become pregnant. It is not known if REGLAN will harm your unborn baby.
- you are breast-feeding. REGLAN can pass into breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you take REGLAN.



Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Metoclopramide tablets, USP and some other medicines may interact with each other and may not work as well, or cause possible side effects. Do not start any new medicines while taking metoclopramide tablets, USP until you talk with your doctor.

Especially tell your doctor if you take:

- another medicine that contains metoclopramide, such as metoclopramide orally disintegrating tablets, or metoclopramide oral syrup
- a blood pressure medicine
- a medicine for depression, especially a Monoamine Oxidase Inhibitor (MAOI)
- insulin
- a medicine that can make you sleepy, such as anti-anxiety medicine, sleep medicines, and narcotics.

If you are not sure if your medicine is one listed above, ask your doctor or pharmacist. Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take metoclopramide tablets, USP?

- Metoclopramide tablets, USP come as a tablet you take by mouth.
- Take metoclopramide tablets, USP exactly as your doctor tells you. Do not change your dose unless your doctor tells you.
- You should not take metoclopramide tablets, USP for more than 12 weeks.
- If you take too many metoclopramide tablets, USP, call your doctor or Poison Control Center right away.

What should I avoid while taking metoclopramide tablets, USP?

- Do not drink alcohol while taking metoclopramide tablets, USP. Alcohol may make some side effects of metoclopramide tablets, USP worse, such as feeling sleepy.
- Do not drive, work with machines, or do dangerous tasks until you know how metoclopramide tablets, USP affect you. Metoclopramide tablets, USP may cause sleepiness.

What are the possible side effects of metoclopramide tablets, USP?

Metoclopramide tablets, USP can cause serious side effects, including:

- **Abnormal muscle movements.** See "What is the most important information I need to know about metoclopramide tablets, USP?"
- **Uncontrolled spasms of your face and neck muscles, or muscles of your body, arms, and legs (dystonia).** These muscle spasms can cause abnormal movements and body positions. These spasms usually start within the first 2 days of treatment. These spasms happen more often in children and adults under age 30.
- **Depression, thoughts about suicide, and suicide.** Some people who take metoclopramide tablets, USP become depressed. You may have thoughts about hurting or killing yourself. Some people who take metoclopramide tablets, USP have ended their own lives (suicide).
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a very rare but very serious condition that can happen with metoclopramide tablets, USP. NMS can cause death and must be treated in a hospital. Symptoms of NMS include: high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating.
- **Parkinsonism.** Symptoms include slight shaking, body stiffness, trouble moving or keeping your balance. If you already have Parkinson's disease, your symptoms may become worse while you are receiving metoclopramide tablets, USP.

ALAVEN PHARMACEUTICAL

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. REGLAN and some other medicines may interact with each other and may not work as well, or cause possible side effects. Do not start any new medicines while taking REGLAN until you talk with your doctor.

Especially tell your doctor if you take:

- another medicine that contains metoclopramide, such as REGLAN ODT, or metoclopramide oral syrup
- a blood pressure medicine
- a medicine for depression, especially a Monoamine Oxidase Inhibitor (MAOI)
- insulin
- a medicine that can make you sleepy, such as anti-anxiety medicine, sleep medicines, and narcotics.

If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take REGLAN?

- REGLAN comes as a tablet you take by mouth.
- Take REGLAN exactly as your doctor tells you. Do not change your dose unless your doctor tells you.
- You should not take REGLAN for more than 12 weeks.
- If you take too much REGLAN, call your doctor or Poison Control Center right away.

What should I avoid while taking REGLAN?

- Do not drink alcohol while taking REGLAN. Alcohol may make some side effects of REGLAN worse, such as feeling sleepy.
- Do not drive, work with machines, or do dangerous tasks until you know how REGLAN affects you. REGLAN may cause sleepiness.

What are the possible side effects of REGLAN?

Reglan can cause serious side effects, including:

- **Abnormal muscle movements.** See "What is the most important information I need to know about REGLAN?"
- **Uncontrolled spasms of your face and neck muscles, or muscles of your body, arms, and legs (dystonia).** These muscle spasms can cause abnormal movements and body positions. These spasms usually start within the first 2 days of treatment. These spasms happen more often in children and adults under age 30.
- **Depression, thoughts about suicide, and suicide.** Some people who take REGLAN become depressed. You may have thoughts about hurting or killing yourself. Some people who take Reglan have ended their own lives (suicide).
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a very rare but very serious condition that can happen with Reglan. NMS can cause death and must be treated in a hospital. Symptoms of NMS include: high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating.
- **Parkinsonism.** Symptoms include slight shaking, body stiffness, trouble moving or keeping your balance. If you already have Parkinson's disease, your symptoms may become worse while you are receiving REGLAN.

5. "What is the most important information I need to know about REGLAN?" is replaced with

"What is the most important information I need to know about metoclopramide tablets, USP?" in proposed medication guide to comply with Teva format.



ALAVEN PHARMACEUTICAL

Call your doctor and get medical help right away if you:

- feel depressed or have thoughts about hurting or killing yourself
- have high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating
- have muscle movements you cannot stop or control
- have muscle movements that are new or unusual

Common side effects of metoprolamide tablets, USP include:

- feeling restless, sleepy, tired, dizzy, or exhausted
- headache
- confusion
- trouble sleeping

You may have more side effects the longer you take metoprolamide tablets, USP and the more metoprolamide tablets, USP you take.

You may still have side effects after stopping metoprolamide tablets, USP. You may have symptoms from stopping (withdrawal) metoprolamide tablets, USP such as headaches, and feeling dizzy or nervous.

Tell your doctor about any side effects that bother you or do not go away. These are not all the possible side effects of metoprolamide tablets, USP.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store metoprolamide tablets, USP?

- Keep metoprolamide tablets, USP at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep metoprolamide tablets, USP in the bottle they came in. Keep the bottle closed tightly.

Keep metoprolamide tablets, USP and all medicines out of the reach of children.

General information about metoprolamide tablets, USP

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use metoprolamide tablets, USP for a condition for which they were not prescribed. Do not give metoprolamide tablets, USP to other people, even if they have the same symptoms that you have. They may harm them.

This Medication Guide summarizes the most important information about metoprolamide tablets, USP. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about metoprolamide tablets, USP that is written for health professionals. For more information, call 1-888-838-2872, MEDICAL AFFAIRS.

Call your doctor and get medical help right away if you:

- feel depressed or have thoughts about hurting or killing yourself
- have high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating
- have muscle movements you cannot stop or control
- have muscle movements that are new or unusual

Common side effects of Reglan include:

- feeling restless, sleepy, tired, dizzy, or exhausted
- headache
- confusion
- trouble sleeping

You may have more side effects the longer you take REGLAN and the more REGLAN you take.

You may still have side effects after stopping REGLAN. You may have symptoms from stopping (withdrawal) REGLAN such as headaches, and feeling dizzy or nervous.

Tell your doctor about any side effects that bother you or do not go away. These are not all the possible side effects of REGLAN.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store REGLAN?

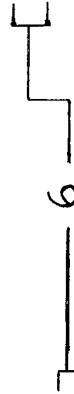
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- Keep REGLAN in the bottle it comes in. Keep the bottle closed tightly.

Keep REGLAN and all medicines out of the reach of children.

General information about REGLAN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REGLAN for a condition for which it was not prescribed. Do not give REGLAN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about REGLAN. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about REGLAN that is written for health professionals. For more information, go to www.alavapharma.com or call 1-888-317-0001.



6. Company contact information is different.



ALAVEN PHARMACEUTICAL

What are the ingredients in metoclopramide tablets, USP?

Active ingredient: metoclopramide

Inactive ingredients: corn starch, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate

This Medication Guide has been approved by the U.S. Food and Drug Administration.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 7/2009

What are the ingredients in REGLAN?

Active ingredient: metoclopramide

Inactive ingredients:
REGLAN 10 mg tablets: magnesium stearate, mannitol, microcrystalline cellulose, stearic acid

REGLAN 5 mg tablets: corn starch, D&C yellow 10 aluminum lake, FD&C blue 1 aluminum lake, lactose, microcrystalline cellulose, silicon dioxide, stearic acid

Manufactured for

Alaven Pharmaceutical LLC, Marietta, GA 30062

Revised June 2009

This Medication Guide has been approved by the U.S. Food and Drug Administration.

7. Inactive ingredients are not identical.
8. Referenced product's manufacturer/distributor and proposed product's manufacturer/distributor are different.
9. Issue date phrasing based on Teva format.

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METOCLOPRAMIDE TABLETS, USP**2204****2203****Rx only****WARNING: TARDIVE DYSKINESIA**

Treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose.

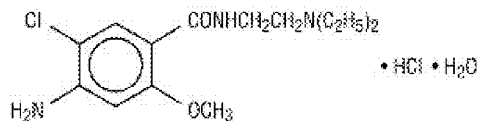
Metoclopramide therapy should be discontinued in patients who develop signs or symptoms of tardive dyskinesia. There is no known treatment for tardive dyskinesia. In some patients, symptoms may lessen or resolve after metoclopramide treatment is stopped.

Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia.

See WARNINGS.

DESCRIPTION

Metoclopramide hydrochloride is a white or practically white, crystalline, odorless or practically odorless powder. It is very soluble in water, freely soluble in alcohol, sparingly soluble in chloroform and practically insoluble in ether. Chemically, it is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Its structural formula is as follows:



$C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$ M.W. 354.3

Each tablet for oral administration contains 5 mg or 10 mg metoclopramide (present as the hydrochloride).

Inactive IngredientsDeleted: ¶
METOCLOPRAMIDE TABLETS USP2204
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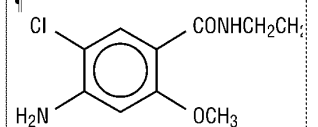
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Corn starch, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

CLINICAL PHARMACOLOGY

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

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Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any, effect on the motility of the colon or gallbladder.

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In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5 mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

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The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like l-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

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Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions, although these are comparatively rare (see **WARNINGS**). Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with transient fluid retention.

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The onset of pharmacological action of metoclopramide is 1 to 3 minutes following an intravenous dose, 10 to 15 minutes following intramuscular administration, and 30 to 60 minutes following an oral dose; pharmacological effects persist for 1 to 2 hours.

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Pharmacokinetics

Metoclopramide is rapidly and well absorbed. Relative to an intravenous dose of 20 mg, the absolute oral bioavailability of metoclopramide is $80\% \pm 15.5\%$ as demonstrated in a crossover study of 18 subjects. Peak plasma concentrations occur at about 1 to 2 hr after a single oral dose. Similar time to peak is observed after individual doses at steady state.

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In a single dose study of 12 subjects, the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5 to 6 hr. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

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Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hr. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide.

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The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to the tissues.

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Renal impairment affects the clearance of metoclopramide. In a study with patients with varying degrees of renal impairment, a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance, and increase in elimination half-life.

The kinetics of metoclopramide in the presence of renal impairment remained linear however.

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The reduction in clearance as a result of renal impairment suggests that adjustment downward of maintenance dosage should be done to avoid drug accumulation.

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Adult Pharmacokinetic Data

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| Parameter | Value |
|------------------------|-------------|
| Vd (L/kg) | ~ 3.5 |
| Plasma Protein Binding | ~ 30% |
| t _{1/2} (hr) | 5 to 6 |
| Oral Bioavailability | 80% ± 15.5% |

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In pediatric patients, the pharmacodynamics of metoclopramide following oral and intravenous administration are highly variable and a concentration-effect relationship has not been established.

There are insufficient reliable data to conclude whether the pharmacokinetics of metoclopramide in adults and the pediatric population are similar. Although there are insufficient data to support the efficacy of metoclopramide in pediatric patients with symptomatic gastroesophageal reflux (GER) or cancer chemotherapy-related nausea and vomiting, its pharmacokinetics have been studied in these patient populations.

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In an open-label study, six pediatric patients (age range, 3.5 weeks to 5.4 months) with GER received metoclopramide 0.15 mg/kg oral solution every 6 hours for 10 doses. The mean peak plasma concentration of metoclopramide after the tenth dose was 2 fold (56.8 mcg/L) higher compared to that observed after the first dose (29 mcg/L) indicating drug accumulation with repeated dosing. After the tenth dose, the mean time to reach peak concentrations (2.2 hr), half-life (4.1 hr), clearance (0.67 L/h/kg), and volume of distribution (4.4 L/kg) of metoclopramide were similar to those observed after the first dose. In the youngest patient (age, 3.5 weeks), metoclopramide half-life after the first and the tenth dose (23.1 and 10.3 hr, respectively) was significantly longer compared to other infants due to reduced clearance. This may be attributed to immature hepatic and renal systems at birth.

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Single intravenous doses of metoclopramide 0.22 to 0.46 mg/kg (mean, 0.35 mg/kg) were administered over 5 minutes to 9 pediatric cancer patients receiving chemotherapy (mean age, 11.7 years; range, 7 to 14 yr) for prophylaxis of cytotoxic-induced vomiting. The metoclopramide plasma concentrations extrapolated to time zero ranged from 65 to 395 mcg/L (mean, 152 mcg/L). The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.4 hr (range, 1.7 to 8.3 hr), 0.56 L/h/kg (range, 0.12 to 1.20 L/h/kg), and 3.0 L/kg (range, 1.0 to 4.8 L/kg), respectively.

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In another study, nine pediatric cancer patients (age range, 1 to 9 yr) received 4 to 5 intravenous infusions (over 30 minutes) of metoclopramide at a dose of 2 mg/kg to control emesis. After the last dose, the peak serum concentrations of metoclopramide ranged from 1060 to 5680 mcg/L. The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.5

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